Exhibit K

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 201280

NDA APPROVAL

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Maureen Oakes, Pharm.D.
Associate Director, Drug Regulatory Affairs
900 Ridgebury Road, P.O. Box 368
Ridgefield, CT 06877

Dear Dr. Oakes:

Please refer to your New Drug Application (NDA) dated and received July 2, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Tradjenta (linagliptin) tablets, 5 mg.

We acknowledge receipt of your amendments dated July 7 and 9, August 2, 3, and 25, September 2, 23, and 30, October 8 and 28, November 1, 12, and 19, and December 1, 17, and 21, 2010; and January 6, 27 (2), 28, and 31, February 4, 7, 11 (2), 14, 16 (2), and 18, March 1 (2), 14, 17, 25, and 29, and April 18, 20, and 29, and May 2, 2011.

This new drug application provides for the use of Tradjenta (linagliptin) tablets as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert and the patient package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry titled *SPL Standard for Content of Labeling Technical Qs and As* at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE-CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate-container labels submitted on March 25, 2011, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 201280**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

ADVISORY COMMITTEE

Your application for Tradjenta (linagliptin) tablets was not referred to an FDA advisory committee because:

- this drug is not a first-in-class anti-diabetic therapy (two other DPP4-inhibitors are currently marketed);
- the indication sought is based on a well-established efficacy endpoint relied upon for approval of other drugs across the 11 classes of anti-diabetic therapies;
- clinical trials assessing efficacy and safety are typical of diabetes programs evaluated by FDA for approval of other anti-diabetic therapies; and
- no unexpected safety concerns were identified in the nonclinical or clinical development program.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to 9 years (inclusive) because the necessary studies are impossible or highly impracticable. This is because there are too few children in this age range with type 2 diabetes mellitus to study.

We are deferring submission of your pediatric studies for ages 10 to 16 years (inclusive) for this application because this product is ready for approval for use in adults and pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. These required studies are listed below.

PMR 1766-1: A randomized, placebo-controlled, dose-finding study under PREA evaluating at least two doses of linagliptin as monotherapy in pediatric patients ages 10 to 16 years (inclusive).

Final Protocol Submission:	by November 30, 2011
Trial Completion:	by February 28, 2014
Final Report Submission:	by August 31, 2014

PMR 1766-2: Deferred randomized and controlled pediatric study under PREA to evaluate efficacy, safety, and pharmacokinetics of linagliptin for the treatment of type 2 diabetes mellitus in pediatric patients ages 10 to 16 years (inclusive) as monotherapy and when added to metformin therapy.

Final Protocol Submission:	by June 30, 2014
Trial Completion:	by March 31, 2017
Final Report Submission:	by September 30, 2017

Submit the protocols to your IND 070963, with a cross-reference letter to this NDA. Submit final reports to this NDA. For administrative purposes, all submissions related to this required pediatric postmarketing study must be clearly designated "**Required Pediatric Assessment(s)**".

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess either a signal of a serious risk of cardiovascular events or a serious risk of hypersensitivity reactions associated with Tradjenta (linagliptin) tablets treatment.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA is not yet sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following study:

PMR 1766-3 An epidemiologic study to compare the risk of severe hypersensitivity and severe cutaneous reactions in type 2 diabetics exposed to linagliptin to the risk in type 2 diabetics exposed to other antidiabetic medications.

The timetable you submitted on April 28, 2011, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	by May 30, 2012
Study Completion:	by November 30, 2018
Final Report Submission:	by June 30, 2019

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of a serious risk of cardiovascular events with anti-diabetic medications, including Tradjenta (linagliptin) tablets, to definitively exclude unacceptable cardiovascular toxicity.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

PMR 1766-4 A randomized, double-blind, placebo-controlled trial evaluating the effect of Tradjenta (linagliptin) tablets on the incidence of major adverse cardiovascular events in patients with type 2 diabetes mellitus.

> The primary objective of this trial is to establish that the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of major adverse cardiovascular events observed with Tradjenta (linagliptin) tablets to that observed in the control group is less than 1.3. Secondary objectives must include an assessment of the long-term effects of Tradjenta (linagliptin) tablets on immunological and , hypersensitivity reactions (including serious skin and/or mucosal reactions), neoplasms, serious hypoglycemia, pancreatitis, and renal safety. For hypersensitivity reactions, especially angioedema, reports should include detailed information on concomitant use of an angiotensin-converting enzyme inhibitor or an angiotensin-receptor blocker. For cases of pancreatitis, serum amylase and/or lipase concentrations with accompanying normal ranges and any imaging reports should be included in the narratives.

The timetable you submitted on April 20, 2011, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	by June 30, 2012
Trial Completion:	by October 31, 2018
Final Report Submission:	by May 31, 2019

Submit the protocol to your IND 070963, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically

report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instructions on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, see the enrollment instructions

and program description details at
http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST-ACTION FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Raymond Chiang, M.S., Regulatory Project Manager, at (301) 796-1940.

Sincerely,

{See appended electronic signature page}

Curtis J. Rosebraugh, M.D., M.P.H.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures:
Package Insert
Patient Package Insert
Container Label – 30-tablet bottle
Container Label – 90-tablet bottle
Container Label – 1000-tablet bottle
Container Label – 7-tablet blister card (sample)
Carton Label – 7 tablet (sample)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CURTIS J ROSEBRAUGH
05/02/2011

Exhibit L

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022200

NDA APPROVAL

Amylin Pharmaceuticals, Inc.
Orville Kolterman, M.D.
Sr. Vice President, Research & Development
9360 Towne Centre Drive, Suite 110
San Diego, CA 92121

Dear Dr. Kolterman:

Please refer to your new drug application (NDA) submitted on May 4, 2009 and received May 5, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for BYDUREON (exenatide extended-release for injectable suspension).

We also refer to our approval letter dated January 27, 2012, which contained the following error: single-dose tray label for professional sample was not attached.

This replacement approval letter incorporates the correction of the error. The effective approval date will remain January 27, 2012, the date of the original approval letter.

We acknowledge receipt of your amendments dated July 28, August 15, 16, 25, September 22, October 4, 20, 24, November 3, and December 8, 2011, and January 10 and 24, 2012.

The July 28, 2011, submission constituted a complete response to our October 18, 2010, action letter.

This new drug application provides for the use of BYDUREON (exenatide extended-release for injectable suspension) as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus in multiple clinical settings.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling. Information on submitting SPL files using

eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your January 24, 2012, submission containing final printed carton and container labels.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to 9 years (inclusive) because the necessary studies are impossible or highly impractical. This is because there are too few children in this age range with type 2 diabetes mellitus to study.

We are deferring submission of your pediatric studies for ages 10 to 17 years (inclusive) until July 2017, because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric study required under section 505B(a) of the Federal Food, Drug, and Cosmetic Act is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. This required study is listed below.

1860-1 A randomized and controlled pediatric study under PREA to evaluate the safety, efficacy, and pharmacokinetics of BYDUREON (exenatide extended-release for injectable suspension) for the treatment of type 2 diabetes mellitus in pediatric patients ages 10-17 years (inclusive).

The timetable you submitted on December 18, 2011, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	04/2012
Study Completion:	01/2017
Final Report Submission:	07/2017

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.
We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of a serious risk of medullary thyroid carcinoma or a signal of a serious risk of adverse cardiovascular events.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1860-2 A 2-year study in mice to determine the reversibility of C-cell hyperplasia, the potential of hyperplasia to progress to neoplasia, and GLP-1 receptor expression on C-cells after 6 months of treatment with exenatide for injectable suspension.

The timetable you submitted on December 18, 2011, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	09/2012
Study Completion:	05/2015
Final Report Submission:	03/2016

1860-3 A study to evaluate and compare GLP-1 receptor expression/density on human, rat, and mouse thyroid C-cells. This should include evaluation of mouse tissue from PMR 1860-2 following exenatide for injectable suspension treatment for 6 months as well as following 1.5 year recovery.

The timetable you submitted on December 18, 2011, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	10/2012
Study Completion:	05/2015
Final Report Submission:	11/2015

1860-4 A study to evaluate the dependence of the GLP-1 receptor for exenatide-induced C-cell hyperplasia and investigate the expression of growth regulatory genes in wild-type and GLP-1 receptor knock-out mice.

The timetable you submitted on December 18, 2011, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	09/2012
Study Completion:	06/2013
Final Report Submission:	12/2013

1860-5 A medullary thyroid carcinoma case series registry of at least 15 years duration to systematically monitor the annual incidence of medullary thyroid carcinoma in the United States and to identify any increase related to the introduction of BYDUREON (exenatide for injectable suspension) into the marketplace. This study will also establish a registry of incident cases of medullary thyroid carcinoma and characterize their medical histories related to diabetes and use of BYDUREON (exenatide for injectable suspension).

The timetable you submitted on December 18, 2011, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	07/2012
Study Completion:	09/2027
Final Report Submission:	09/2028

Finally, there have been signals of a serious risk of cardiovascular events with some medications developed for the treatment of type 2 diabetes mellitus, and available data have not definitively excluded the potential for this serious risk with BYDUREON (exenatide extended-release for injectable suspension). We have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of a serious risk of cardiovascular events with antidiabetic medications, including BYDUREON (exenatide extended-release for injectable suspension). Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1860-6 A randomized, double blind, placebo-controlled trial evaluating the effect of BYDUREON (exenatide extended-release for injectable suspension) on the incidence of major adverse cardiovascular events (MACE) in subjects with type 2 diabetes mellitus (T2DM). The trial must also assess adverse events of interest including the long-term effects of BYDUREON (exenatide extended-release for injectable suspension) on potential biomarkers of medullary thyroid carcinoma (e.g., serum calcitonin) as well as long-term effects on thyroid neoplasms, pancreatitis (including hemorrhagic and necrotizing forms), pancreatic cancer, serious injection site reactions (including nodules), allergic/hypersensitivity events, serious hypoglycemia, and renal disorders.

The timetable you submitted on December 18, 2011, states that you will conduct this trial according to the following schedule:

Trial Completion:	07/2018
Final Report Submission:	12/2018

Submit the protocols to your IND 067092, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. The details of the REMS requirements were outlined in our REMS notification letter dated February 16, 2010.

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for BYDUREON (exenatide extended-release for injectable suspension) to ensure the benefits of the drug outweigh the risks of medullary thyroid carcinoma and acute pancreatitis, including hemorrhagic and necrotizing pancreatitis.

Although we continue to believe that a REMS is necessary to ensure that the benefits of BYDUREON (exenatide extended-release for injectable suspension) outweigh its risks, upon further consideration, we have determined that a Medication Guide is not necessary as part of the REMS to ensure the benefits of the drug outweigh the risks described above because maintaining the Medication Guide as part of the approved labeling is adequate to address the serious and significant public health concern and meets the standard in 21 CFR 208.1. Therefore, it is no

longer necessary to include the Medication Guide as an element of the approved REMS to ensure that the benefits of BYDUREON (exenatide extended-release for injectable suspension) outweigh its risks.

Your proposed REMS, submitted on January 24, 2012, and appended to this letter, is approved. The REMS consists of a communication plan and a timetable for submission of assessments of the REMS.

Your REMS must be fully operational before you introduce BYDUREON (exenatide extended-release for injectable suspension) into interstate commerce.

The REMS assessment plan should include, but is not limited to, the following:

1. The 1-year, 2-year, and 7th-year REMS assessment reports will include the following:

    a) The results of surveys assessing healthcare providers' understanding of the critical content related to pancreatitis and medullary thyroid cancer. The assessment will include healthcare providers' awareness of appropriate BYDUREON (exenatide extended-release for injectable suspension) patient population characteristics, the potential risk for medullary thyroid carcinoma, and the need for prompt evaluation of patients who develop symptoms suggestive of pancreatitis.

    b) The results of surveys assessing healthcare providers' identification and treatment of medullary thyroid carcinoma and acute pancreatitis after initiation of BYDUREON (exenatide extended-release for injectable suspension).

    c) The results of case series review of targeted safety surveillance of spontaneously reported cases of acute pancreatitis.

    d) The percentage of targeted prescribers who are presented with the Highlighted Information for Prescribers via sales specialists or medical information department.

    e) An analysis of use data establishing the extent of first-line use of BYDUREON (exenatide extended-release for injectable suspension).

    f) An evaluation of the extent to which the elements of the REMS are meeting the goals of the REMS and whether modifications to the elements or goals are needed.

2. The 1-year REMS assessment report will include the number of letters sent via email, standard mail, and facsimile, and the dates the letters were sent. For the letters sent via email, include the number of letters sent via standard mail because the healthcare provider did not have an email address, and the number sent because the email was undeliverable. For letters sent via email, include the number of letters successfully delivered, and the number of email letters opened by the recipients.

3. Information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. With respect to any such postapproval study, you must include the status of such study, including whether any difficulties completing the study have been encountered. With respect to any such postapproval clinical trial, you must include the status of such clinical trial, including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to requirements under subsections (i) and (j) of section 402 of the Public Health Service Act. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) including any material or significant updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in section 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA.

You should update the REMS supporting document to include the following:

- a detailed document outlining the final methodology and content of the healthcare provider survey at least 90 days prior to initiating the conduct of the survey. Three healthcare provider surveys will be conducted in accordance with the timeline for submission of assessments of the REMS: 1 year, 2 years, and in the 7th year.

- a detailed document outlining the final methodology for conducting case review evaluations of pancreatitis at least 90 days prior to initiating the evaluation. Three evaluations will be conducted in accordance with the timeline for submission of assessments of the REMS: 1 year, 2 years, and in the 7th year.

- any additional instruments and methodology for your REMS assessments that are not included in the REMS supporting document.

Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

NDA 022200 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY)

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

Prominently identify the submission containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

NDA 022200 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 022200
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE) FOR NDA 022200
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

We request that for a period of two years, you submit all cases of hemorrhagic and/or necrotizing pancreatitis and all cases of suspected or confirmed reports of acute pancreatitis with an outcome of death as 15-day alert reports, and that you provide analyses of clinical trial and post-marketing reports of pancreatitis, including hemorrhagic and/or necrotizing pancreatitis, as adverse events of special interest in your periodic safety update reports.

If you have any questions, please call Pooja Dharia, Pharm.D., Regulatory Project Manager, at (301) 796-5332.

Sincerely,

{See appended electronic signature page}

Mary Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURES:
Package Insert
Medication Guide
Instructions for Use
Carton and Container Labeling
REMS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARY H PARKS
01/27/2012

Exhibit M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022271

NDA APPROVAL

Takeda Pharmaceuticals U.S.A., Inc.
Attention: Sandra D. Cosner, RPh
Associate Director, Regulatory Affairs
One Takeda Parkway
Deerfield, IL 60015

Dear Ms. Cosner:

Please refer to your New Drug Application (NDA) dated and received December 27, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Nesina (alogliptin) tablets, 6.25 mg, 12.5 mg, and 25 mg.

We acknowledge receipt of your amendments dated February 20 and 22, March 21, April 1 and 24, May 7, 9, 16, and 30, June 26, July 22 and 31, August 5, 11, 25, and 29, September 5, October 3, 16, 17, and 29, November 10, 13, and 18, and December 17 and 18, 2008, and January 19 and 21, March 4, 10, 16, and 25, April 9, May 6, 20, and 28, August 31, and October 28, 2009, and January 21, February 11, March 15, April 13, May 7, June 21, and July 21, 2010, and May 25, July 13 and 25, August 25, September 14, October 5, 6, and 11, November 7, 17, and 22, and December 2, 7, and 20, 2011, and January 20 (2), 23, and 24 (2), February 1, 9, 13, 14, and 22 (2), March 6, 8, 13, 22, 23, 26, 27, 28, and 30, April 4, 5, 19, 27, and 30, May 30, July 12 and 26, August 1 (2), 2, 6, 14, and 27, September 13 and 25, October 5, 10, 11, and 23, November 1, 7, 9, 15, 16, 27, and 30, and December 18, 2012, and January 7 (2), 9 (2), 11, and 17, 2013. We also acknowledge receipt of your emails dated January 24 and 25, 2013 that included the agreed-upon labeling.

The submission dated July 26, 2012, constituted a complete response to our action letter dated April 25, 2012.

This new drug application provides for the use of Nesina (alogliptin) tablets as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

We have completed our review of this application. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert and text for Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE-CONTAINER LABELS

Submit final printed carton and immediate-container labels that are identical to the enclosed carton and immediate-container labels submitted on **January 17, 2013**, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 022271**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

EXPIRY DATING PERIOD

A 30-month expiry dating period is granted for Nesina (alogliptin) 6.25 mg tablets and a 36-month expiry dating period is granted for Nesina 12.5 mg and 25 mg tablets when stored at 25°C (77°F) with excursions permitted to 15°-30°C (59°-86°F).

ADVISORY COMMITTEE

Your application for Nesina was not referred to an FDA advisory committee because this drug is not the first in its class and outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 through 9 years because the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age group **and** is not likely to be used in a substantial number of pediatric patients in this group.

We are deferring submission of your pediatric study for ages 10 to 17 years for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. The required studies are listed below.

2007-1: A clinical pharmacology study in pediatric patients with type 2 diabetes to evaluate the pharmacokinetics of alogliptin and to determine the dose(s) for the subsequent Phase 3 studies that will be conducted under the Pediatric Research Equity Act (PREA) to evaluate the efficacy and safety of alogliptin for the treatment of type 2 diabetes mellitus in pediatric patients ages 10 to 17 years (inclusive). At least 25% of randomized subjects will be 10-13 years of age.

Study Completion:	December 31, 2013
Final Report Submission:	June 30, 2014

2007-2: A 52-week, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of alogliptin when added on to metformin in pediatric patients ages 10 to 17 years (inclusive) with type 2 diabetes mellitus. At least 30% of randomized subjects will be 10-14 years of age, and at least one-third and not more than two-thirds of subjects in both age subsets (10-14 years and 15-17 years) will be female.

Final Protocol Submission:	July 31, 2015
Study Completion:	July 31, 2019
Final Report Submission:	January 31, 2020

2007-3: A 52-week, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of alogliptin in pediatric patients ages 10 through 17 years (inclusive) with type 2 diabetes mellitus . At least 30% of randomized subjects will be 10-14 years of age, and at least on-third and not more than two-thirds of subjects in both age subsets (10-14 years and 15-17 years) will be female.

Final Protocol Submission:	July 31, 2015
Study Completion:	November 30, 2020
Final Report Submission:	May 31, 2021

Submit the protocols to your IND 069707, with a cross-reference letter to this NDA.

Reports of these required pediatric postmarketing studies must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess signals of serious risks of hepatotoxicity, acute pancreatitis, hypersensitivity reactions, cardiovascular events, serious hypoglycemia, and renal impairment in patients treated with Nesina (alogliptin).

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

2007-4: An assessment and analysis of spontaneous reports of serious hepatic abnormalities, fatal pancreatitis, hemorrhagic/necrotizing pancreatitis, and severe hypersensitivity reactions (angioedema, anaphylaxis, Stevens Johnson Syndrome) in patients treated with Nesina (alogliptin). Specialized follow-up should be obtained on these cases to collect additional information on the events. This enhanced pharmacovigilance should continue for a period of 5 years from the date of approval for reports of fatal pancreatitis and hemorrhagic/necrotizing pancreatitis, and

10 years from the date of approval for reports of serious hepatic abnormalities and severe hypersensitivity reactions.

The timetable you submitted on January 21, 2013, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	October 31, 2013
Interim Report Submissions:	March 31, 2014
	March 31, 2015
	March 31, 2016
	March 31, 2017
	March 31, 2018
	March 31, 2019
	March 31, 2020
	March 31, 2021
	March 31, 2022
Study Completion:	January 31, 2023
Final Report Submission:	September 30, 2023

Finally, there have been signals of a serious risk of cardiovascular events with some medications developed for the treatment of type 2 diabetes mellitus, and available data have not definitively excluded the potential for this serious risk with Nesina (alogliptin). We have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of a serious risk of major adverse cardiovascular events with antidiabetic medications, including Nesina (alogliptin). Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

2007-5: A randomized, double-blind, placebo-controlled trial evaluating the effect of Nesina (alogliptin) on the incidence of major adverse cardiovascular events in patients with type 2 diabetes mellitus. The primary objective of the trial is to establish that the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of major adverse cardiovascular events observed with Nesina (alogliptin) to that observed in the control group is less than 1.3. The long-term effects of Nesina (alogliptin) on hepatotoxicity, hypersensitivity reactions (including severe cutaneous reactions), serious hypoglycemia, pancreatitis, and renal safety will also be evaluated. The trial must include at least 200 Nesina (alogliptin)-treated patients with moderate renal impairment and 100 Nesina (alogliptin)-treated patients with severe renal impairment

The timetable you submitted on January 21, 2013, states that you will conduct this trial according to the following schedule:

Trial Completion:	December 31, 2013
Final Report Submission:	September 30, 2014

Submit the protocol to your IND 069707, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

METHODS VALIDATION

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST-ACTION FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Richard Whitehead, Regulatory Project Manager, at (301) 796-4945.

Sincerely,

{See appended electronic signature page}

Curtis Rosebraugh, M.D., M.P.H.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures:
Prescribing Information
Medication Guide
Carton and Container Labels

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CURTIS J ROSEBRAUGH

01/25/2013

I am approving the single-entity alogliptin first, before approving the combination products containing alogliptin.

Exhibit N

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022200/S-008

SUPPLEMENT APPROVAL

Amylin Pharmaceuticals, LLC
Attention: Cindy Cao, Ph.D.
Associate Director, CV & Metabolics
Global Regulatory & Safety Sciences - US
P.O. Box 4000 (Mail Stop: D22-06)
Princeton, NJ 08543-4000

Dear Dr. Cao:

Please refer to your Supplemental New Drug Application (sNDA) dated August 29, 2013, received August 30, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Bydureon (exenatide extended-release for injectable suspension).

We acknowledge receipt of your amendments dated October 17, November 14, December 11, 16, and 23, 2013, and February 5, and 24, 2014.

This "Prior Approval" supplemental new drug application proposes a manually operated, single-use, dual-chamber pen presentation of Bydureon (exenatide extended release for injectable suspension).

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, Medication Guide, Instruction for Use for single-dose tray presentation, and Instructions for Use for pen presentation) with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at

http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the enclosed carton and immediate container labels, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008).* Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA022200/S-008**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf.

For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

Sincerely,

{See appended electronic signature page}

Jean-Marc Guettier, M.D.
Director (Acting)
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURES:
Prescribing Information
Medication Guide
Instruction for Use for single-dose tray presentation (version approved on January 27, 2012)
Instructions for Use for pen presentation
Carton and Container Labeling for pen presentation

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JEAN-MARC P GUETTIER
02/28/2014

Exhibit O

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125431/0

BLA APPROVAL

GlaxoSmithKline LLC
Attention: Susan Watts, Ph.D.
Director, Therapeutic Groups
Five Moore Drive
P.O. Box 13398
Research Triangle Park, NC 27709-3398

Dear Dr. Watts:

Please refer to your Biologics License Application (BLA) dated and received January 14, 2013, submitted under section 351(a) of the Public Health Service Act for Tanzeum (albiglutide) for injection, for subcutaneous use.

We acknowledge receipt of your amendments dated February 13, 18, and 27, March 5 and 7, April 8, 10, 19, and 26, May 15 (2), 20, 24, and 29, June 4, 7, 10, 14 (3), 18, 19, and 28, July 12, August 5, 8, 12, 16, 19, 23, and 30, September 2 and 30, October 4, 8, 10, and 31, November 8 (2), 18, 22, and 28, and December 12, 13, 18 and 20 (2), 2013, and January 8, 10, 21, and 22, February 11 and 25, March 7, 14, 25, and 28, and April 8, 9 (2), 10, and 11, 2014.

LICENSING

We have approved your BLA for Tanzeum (albiglutide) for injection, for subcutaneous use effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Tanzeum (albiglutide) under your existing Department of Health and Human Services U.S. License No. 1727. Tanzeum (albiglutide) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture Tanzeum (albiglutide) drug substance at GlaxoSmithKline LLC in Conshohocken, Pennsylvania. The final formulated product will be manufactured, filled, assembled into auto-injectors, labeled, and packaged at (b) (4) (b) (4) You may label your product with the proprietary name, Tanzeum, and will market it in 30 mg or 50 mg in a single-dose pen for injection.

DATING PERIOD

The dating period for Tanzeum (albiglutide) shall be 12 months from the date of manufacture when stored at 2-8 °C. The date of manufacture shall be defined as the date of (b) (4) (b) (4). The dating period for your drug substance shall be (b) (4) (b) (4) Results of ongoing stability should be submitted throughout the dating period, as they become available, including the results of stability studies from the first three production lots. We have approved the stability protocol in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of Tanzeum to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1, requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

Any changes in the manufacturing, testing, packaging, or labeling of Tanzeum, or in the manufacturing facilities, will require the submission of information to your biologics license application for our review and written approval, consistent with 21 CFR 601.12.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert and Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)". Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Product Correspondence – Final Printed Carton and Container Labels for approved BLA 125431/0**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with final printed labeling (FPL) that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

ADVISORY COMMITTEE

Your application for Tanzeum was not referred to an FDA advisory committee because outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to 9 years (inclusive) because necessary studies are impossible or highly impracticable. This is because there are too few children in this age range with type 2 diabetes mellitus to study.

We are deferring submission of your pediatric study for ages 10 to 17 years (inclusive) for this application because this product is ready for approval for use in adults and the pediatric study have not been completed.

Your deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 601.28 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. This required study is listed below.

1. A randomized and controlled pediatric study under PREA to evaluate the safety, efficacy, and pharmacokinetics of Tanzeum (albiglutide) for the treatment of type 2 diabetes mellitus in pediatric patients ages 10-17 years (inclusive).

Final Protocol Submission:	October 2014
Study Completion	April 2020
Final Report Submission:	October 2020

Submit the protocol to your IND 065177, with a cross-reference letter to this BLA.
Reports of this required pediatric postmarketing study must be submitted as a BLA or as a supplement to your approved BLA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess either a signal of a serious risk of cardiovascular events or a serious risk of medullary thyroid carcinoma associated with Tanzeum (albiglutide).

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

2. A medullary thyroid carcinoma case series registry of at least 15 years duration to systematically monitor the annual incidence of medullary thyroid carcinoma in the United States and to identify any increase related to the introduction of Tanzeum (albiglutide) into the marketplace. This study will also establish a registry of incident cases of medullary thyroid carcinoma and characterize their medical histories related to diabetes and use of Tanzeum (albiglutide).

The timetable you submitted on April 10, 2014, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	October 2014
Study Completion:	December 2029
Final Report Submission:	December 2030

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of a serious risk of cardiovascular events with anti-

diabetic medications, including Tanzeum (albiglutide) for injection, for subcutaneous use, to definitively exclude unacceptable cardiovascular toxicity.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

3. A randomized, double blind, placebo-controlled trial evaluating the effect of Tanzeum (albiglutide) on the incidence of major adverse cardiovascular events (MACE) in subjects with type 2 diabetes mellitus. The primary objective of the trial should be to demonstrate that the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of MACE (non-fatal myocardial infarction, non-fatal stroke, cardiovascular death) observed with albiglutide to that observed in the placebo group is less than 1.3. This trial must also assess the following adverse events: development of thyroid cancer, hematologic malignancies, pancreatic cancer, pancreatitis, overall injection site reactions, immunological reactions including serious hypersensitive reactions, serious hypoglycemia events, hepatic events, hepatic enzyme elevations (including gamma-glutamyl transpeptidase [GGT]), serious gastrointestinal events, appendicitis, atrial fibrillation/flutter, pneumonia, worsening renal function, and diabetic retinopathy.

The timetable you submitted on April 10, 2014, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	September 2014
Trial Completion:	May 2019
Final Report Submission:	November 2019

Submit the protocols to your IND 065177, with a cross-reference letter to this BLA. Submit all final reports to your BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: "**Required Postmarketing Protocol Under 505(o)**," "**Required Postmarketing Final Report Under 505(o)**," "**Required Postmarketing Correspondence Under 505(o)**."

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies

or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4. A study evaluating gallbladder ejection fractions in albiglutide treated subjects to further characterize the effect of albiglutide on gallbladder motility.

The timetable you submitted on April 10, 2014, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	April 2015
Study Completion:	August 2016
Final Report Submission:	February 2017

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

5. To develop, validate, and implement an ultra-performance liquid chromatography (UPLC) analytical method to assess purity for release and stability of drug substance and drug product.

The timetable you submitted on April 10, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission:	August 2015

6. To develop, validate, and implement a neonatal Fc receptor binding assay to monitor functionality of human albumin portion of drug substance and drug product for release and stability.

The timetable you submitted on April 10, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission:	May 2015

7. To conduct studies to develop an understanding of the mechanism of low endotoxin recovery in the formulated drug substance and drug product. In addition, develop and validate a reliable endotoxin test for the albiglutide drug product in-process and release samples and include worst-case hold conditions in

the relevant containers. Provide the information and data in accordance with 21CFR601.12.

The timetable you submitted on April 10, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission: April 2015

8. To conduct a bulk drug substance stability study using samples stored for the desired shelf life in the (b) (4). Stability testing should be performed on drug substance aliquots removed following (b) (4) (b) (4).

The timetable you submitted on April 10, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission: January 2015

9. To implement CAPAs (corrective action/preventative action) to establish a (b) (4) for bulk drug substance.

The timetable you submitted on April 10, 2014, states that you will conduct this study according to the following schedule:

Implementation date: June 2015
Final Report Submission: August 2015

Submit clinical protocols to your IND 065177 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for Tanzeum (albiglutide) to ensure the

benefits of the drug outweigh the potential risk of medullary thyroid carcinoma and the risk of acute pancreatitis.

We have also determined that a communication plan is necessary to support implementation of the REMS

Your proposed REMS, emailed to us on April 13, 2014, and appended to this letter, is approved. The REMS consists of a communication plan and a timetable for submission of assessments of the REMS.

Your REMS must be fully operational before you introduce Tanzeum (albiglutide) into interstate commerce.

At least 24 hours prior to issuing the Dear Healthcare Provider letter(s) that are required as part of the REMS described above, submit an electronic copy of the letter to this NDA, and to CDERMedWatchSafetyAlerts@fda.hhs.gov, and to the following address:

MedWatch program
Office of Special Health Issues
Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

The REMS assessment plan should include, but is not limited to, the following:

a) REMS communication plan activities:
   (1) Number of healthcare providers and professional societies targeted by the REMS.
   (2) Number of REMS letters sent to healthcare providers and professional societies via email, standard mail, and facsimile, and the dates the letters were sent. Include the number of letters sent via standard mail because the healthcare providers did not have an email address, and the number sent because the email was undeliverable. For letters sent via email, include the number of letters successfully delivered, and the number of email letters opened by the recipients.
   (3) Number of REMS Factsheets distributed to healthcare providers during the 12 months after product launch.
   (4) Date when REMS website went live and number of total and unique site visits during the assessment period.

b) Evaluation of healthcare providers' understanding of:
   (1) The potential risk of medullary thyroid cancer.
   (2) The risk of pancreatitis.

(3) The need for prompt evaluation of patients who develop symptoms suggestive of pancreatitis.

(4) Appropriate albiglutide patient population characteristics.

c) Safety surveillance:

(1) Albiglutide utilization information including, but not limited to, indication and type of HCP (i.e., endocrinologist, general practitioner, internist, etc.).

(2) Evaluation and postmarketing case reports of pancreatitis.

(3) Evaluation and postmarketing case reports of medullary thyroid cancer.

(4) Any other relevant data and analysis employed to assess if the albiglutide REMS is meeting its goals.

The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether 1 or more such goals or such elements should be modified.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

BLA 125431 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY)

Prominently identify the submission containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

BLA 125431 REMS ASSESSMENT

NEW SUPPLEMENT FOR BLA 125431
PROPOSED REMS MODIFICATION

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR BLA 125431
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send 5 copies of REMS-related submissions.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). You should submit postmarketing adverse experience reports to:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA-3486 to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
5901-B Ammendale Road
Beltsville, MD 20705-1266

Biological product deviations, sent by courier or overnight mail, should be addressed to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4206
Silver Spring, MD 20903

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

PDUFA V APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V ('the Program'). The PDUFA V Commitment

Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a PDUFA V applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

If you have any questions, call Raymond Chiang, Regulatory Project Manager, at (301) 796-1940.

Sincerely,

{See appended electronic signature page}

Curtis J. Rosebraugh, M.D., M.P.H.
Director
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling
Carton and Container Labeling
REMS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CURTIS J ROSEBRAUGH
04/15/2014

Exhibit P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125469/0

BLA APPROVAL

Eli Lilly and Company
Attention: Kenneth Mace, PhD
Advisor, Global Regulatory Affairs-US
Lilly Corporate Center, DC 2543
Indianapolis, IN 46285

Dear Dr. Mace:

Please refer to your Biologics License Application (BLA) dated September 17, 2014, received September 18, 2014, submitted under section 351(a) of the Public Health Service Act for Trulicity (dulaglutide).

We also refer to our approval letter dated September 18, 2014, which contained errors in the Manufacturing Locations and Dating Period sections of the letter.

This replacement approval letter incorporates the correction of the errors. The effective approval date will remain September 18, 2014, the date of the original approval letter.

We acknowledge receipt of your amendments dated October 8 and 14, November 22, December 6, 2013, and January 10 and 13 (2), February 6, 21, and 28, April 4, 11, 14, 17, 18, 21 (3), 24, and 29, May 5, 6, 8, 27, and 30, June 9, 11, 13, 18, 24, 27, and 30, July 17, August 5, 25, and 27, and September 9 and 18, 2014.

We also acknowledge receipt of your email dated September 18, 2014, which includes the agreed-upon labeling.

LICENSING

We have approved your BLA for Trulicity (dulaglutide) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Trulicity, under your existing department of Health and Human Services U.S. License No. 1891. Trulicity is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture dulaglutide drug substance at Eli-Lilly S.A, Kinsale, Ireland (FEI number 3002806888). The final formulated product will be manufactured and filled at Eli Lilly and Company, Indianapolis, IN (FEI number 1819470) and [(b) (4)] (FEI numbe[(b) (4)]). The semi-finished syringes will be assembled into pre-filled syringes, labeled, and packaged at [(b) (4)] (FEI [(b) (4)]. The semi-finished syringes will be assembled into pre-filled pens, labeled, and packaged at Eli Lilly and Company, Indianapolis, IN (FEI number 1819470). You may label your product with the proprietary name, Trulicity, and will market it in 1.5 mg/0.5 mL and 0.75 mg/0.5 mL single dose pre-filled syringes and pre-filled pens.

DATING PERIOD

The dating period for Trulicity shall be 24 months from the date of manufacture when stored at 2-8°C. The date of manufacture shall be defined as the [(b) (4)] The dating period for your drug substance shall be [(b) (4)] months from the date of manufacture when stored at [(b) (4)]

FDA LOT RELEASE

You are not currently required to submit samples of future lots of Trulicity to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2a (specified product). We will continue to monitor compliance with 21 CFR 610.1, requiring completion of tests for conformity with standards applicable to each product prior to release of each lot

Any changes in the manufacturing, testing, packaging, or labeling of Trulicity, or in the manufacturing facilities, will require the submission of information to your BLA for our review and written approval, consistent with 21 CFR 601.12.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

WAIVER OF HIGHLIGHTS SECTION

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert and Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your August 27, 2014, submission containing final printed carton and container labels

ADVISORY COMMITTEE

Your application for Trulicity (dulaglutide) was not referred to an FDA advisory committee because this biologic is not first in class, the safety profile is similar to that of other drugs approved for this indication, and the application did not raise significant safety or efficacy issues that were unexpected for a biologic of this class.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to 9 years (inclusive) for this application because necessary studies are impossible or highly impracticable. This is because there are too few children in this age range with type 2 diabetes mellitus to study.

We are deferring submission of your pediatric studies for ages 10 to 17 years (inclusive), because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 601.28 and section 505B(a)(3)(B) of the FDCA. These required studies are listed below.

2781-1 A 26-week randomized, double-blind, placebo controlled study of the safety, efficacy, and pharmacokinetics (PK) of Trulicity (dulaglutide) for the treatment of type 2 diabetes mellitus in pediatric patients ages 10 to 17 years (inclusive) with or without concomitant metformin therapy, followed by a 26-week open-label extension. As part of this study, sparse blood samples for population PK and exposures-response analysis will be collected. This trial should not be initiated until after the data from the juvenile toxicity study have been submitted to and reviewed by the Agency.

Final Protocol Submission:	February 2016
Study Completion:	August 2022
Final Report Submission:	January 2023

2781-2 A study to evaluate dulaglutide toxicity in immature rats.

Study Completion:	January 2015
Final Report Submission:	March 2015

Submit the protocols to your IND 070930, with a cross-reference letter to this BLA.

Reports of these required pediatric postmarketing studies must be submitted as a BLA or as a supplement to your approved BLA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of a serious risk of medullary thyroid carcinoma associated with Trulicity (dulaglutide).

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

2781-3 A medullary thyroid carcinoma registry-based case series of at least 15 years duration to systematically monitor the annual incidence of medullary thyroid carcinoma in the United States and to identify any increase related to the introduction of Trulicity (dulaglutide) into the marketplace. This study will also establish a registry of incident cases of medullary thyroid carcinoma and characterize their medical histories related to diabetes and use of Trulicity (dulaglutide).

The timetable you submitted by email on September 3, 2014, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	June 2015
Study Completion:	December 2030
Final Report Submission:	March 2032

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to:

- Assess signals of a serious risk of worsening renal function and other serious adverse events in patients with renal impairment treated with Trulicity (dulaglutide).
- Assess signals of a serious risk of major adverse cardiovascular events (MACE) with Trulicity (dulaglutide). There have been signals of a serious risk of cardiovascular events with some other medications developed for the treatment of type 2 diabetes mellitus and available data have not definitively excluded the potential for this serious risk with Trulicity (dulaglutide).
- Assess signals of the serious risks of pancreatic cancer, pancreatitis, immune-mediated reactions (including serious hypersensitivity reactions), serious hypoglycemic events, hepatic events, serious gastrointestinal events, clinically significant supraventricular arrhythmias and clinically significant conduction disorders.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

2781-4 A 26-week randomized, controlled trial comparing once weekly Trulicity (dulaglutide), 0.75 mg and 1.5 mg, with insulin glargine on glycemic control in patients with type 2 diabetes mellitus and moderate or severe renal impairment, with a 26-week controlled extension.

The timetable you submitted by email on September 3, 2014, states that you will conduct this study according to the following schedule:

Trial Completion:	November 2016
Final Report Submission:	May 2017

2781-5 A randomized, double-blind, placebo-controlled trial evaluating the effect of Trulicity (dulaglutide) on the incidence of major adverse cardiovascular events (MACE) in patients with type 2 diabetes mellitus. The primary objective of the trial should be to demonstrate that the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of MACE (non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death) observed with dulaglutide to that observed in the placebo group is less than 1.3. The trial must also assess the following adverse events: thyroid cancer, pancreatic cancer, pancreatitis, immune-mediated reactions (including serious hypersensitivity reactions), serious hypoglycemic events, hepatic events, serious gastrointestinal events, clinically significant supraventricular arrhythmias, clinically significant conduction disorders and worsening renal function.

The timetable you submitted by email on September 17, 2014, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	June 2015
Trial Completion:	June 2019
Final Report Submission:	March 2020

Submit the protocols to your IND 070930, with a cross-reference letter to this BLA. Submit all final reports to your BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: "**Required Postmarketing Protocol Under 505(o)**," "**Required Postmarketing Final Report Under 505(o)**," "**Required Postmarketing Correspondence Under 505(o)**."

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

2781-6 To re-evaluate dulaglutide drug substance lot release and stability specifications after 30 lots have been manufactured using the commercial manufacturing process.

The timetable you submitted by email on September 3, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission: June 2018

2781-7 To re-evaluate dulaglutide drug product lot release and stability specifications after 30 lots have been manufactured using the commercial manufacturing process.

The timetable you submitted by email on September 3, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission: June 2018

2781-8 To conduct drug substance and drug product specific leachable and extractable studies on the (b) (4) used during manufacturing. The drug substance and drug product manufacturing processes will be optimized, as needed, based on the results.

The timetable you submitted by email on September 3, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission: June 2016

2781-9 To reassess the dulaglutide drug substance and drug product control strategy, and the reference standard qualification/requalification programs, with regards to Fc region modifications and their impact on PK, including neonatal Fc binding.

The timetable you submitted by email on September 3, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission: December 2016

2781-10 Provide data from one additional (b) (4) batch to support the (b) (4) hour hold time limit (b) (4) Provide this data in the first annual report.

The timetable you submitted by email on September 3, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission: November 2015

2781-11 Provide summary data from performance qualification shipping studies for shipment of the SFS and PFS from (b) (4) to Eli Lilly in the summer and winter. Provide this data in the first annual report.

The timetable you submitted by email on September 3, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission: November 2015

2781-12 Explore alternative endotoxin test methods and develop a more suitable endotoxin release test for dulaglutide drug substance and drug product.

The timetable you submitted by email on September 4, 2014, states that you will conduct this study according to the following schedule:

Final Protocol Submission: March 2015
Final Report Submission: December 2016

Submit clinical protocols to your IND 070930 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)].

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for Trulicity (dulaglutide) to ensure the benefits of the drug outweigh the potential risk of medullary thyroid carcinoma and the risk of pancreatitis.

We have also determined that a communication plan is necessary to support implementation of the REMS.

Your proposed REMS, submitted on September 18, 2014, and appended to this letter, is approved. The REMS consists of a communication plan and a timetable for submission of assessments of the REMS.

Your REMS must be fully operational before you introduce Trulicity (dulaglutide) into interstate commerce.

The REMS assessment plan should include, but is not limited to, the following:

1. REMS communication plan activities:
    a. Number of healthcare providers (HCPs) and professional societies targeted by the REMS.
    b. Number of REMS letters sent to HCPs and professional societies via email, standard mail, and facsimile, and the dates the letters were sent. Include the number of letters sent via standard mail because the HCP did not have an email address, and the number sent because the email was undeliverable. For letters sent via email, include the number of letters successfully delivered, and the number of email letters opened by the recipients.
    c. Number of REMS Factsheets distributed to HCPs during the 12 months after product launch.
    d. Date when REMS website went live and number of total and unique site visits during the assessment period.
2. Evaluation of HCPs' understanding of:
    a. The potential risk of medullary thyroid carcinoma (MTC)
    b. The risk of pancreatitis
    c. The need for prompt evaluation of patients who develop symptoms suggestive of pancreatitis
    d. Identification and treatment of pancreatitis after initiation of dulaglutide
    e. Appropriate dulaglutide patient population characteristics
3. Safety surveillance
    a. Dulaglutide utilization information including, but not limited to, indication and type of HCP (i.e., endocrinologist, general practitioner, internist, etc.)
    b. Evaluation and post-marketing case reports of pancreatitis

c. Evaluation and post-marketing case reports of medullary thyroid carcinoma (MTC)

d. Any other relevant data and analysis employed to assess if the dulaglutide REMS is meeting its goals

e. The evaluation shall include, with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether 1 or more such goals or elements should be modified. If a REMS modification is needed, provide an overview of the impact of the REMS modification on stakeholders and any additional evaluations needed as part of the REMS assessment plan to assess the impact of the proposed REMS modification.

The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether 1 or more such goals or such elements should be modified.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

BLA 125469 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY)

Prominently identify the submission containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

BLA 125469 REMS ASSESSMENT

NEW SUPPLEMENT FOR BLA 125469
PROPOSED REMS MODIFICATION

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR BLA 125469
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send 5 copies of REMS-related submissions.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). You should submit postmarketing adverse experience reports to:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA-3486 to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
5901-B Ammendale Road
Beltsville, MD 20705-1266

Biological product deviations, sent by courier or overnight mail, should be addressed to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4206
Silver Spring, MD 20903

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

PDUFA V APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V ('the Program'). The PDUFA V Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals,

complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a PDUFA V applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

If you have any questions, call Abolade (Bola) Adeolu, Regulatory Project Manager, at (301) 796-4264.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, MD
Deputy Director
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURES:
Package Insert
Medication Guide
Instructions for Use
Carton and Container Labeling
REMS

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/s/

MARY H PARKS
09/18/2014

Exhibit Q

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206321/S-001

SUPPLEMENT APPROVAL

Novo Nordisk, Inc.
Attention: Michelle Thompson
Senior Director, Regulatory Affairs
P.O. Box 846
800 Scudders Mill Road
Plainsboro, NJ 08536

Dear Ms. Thompson:

Please refer to your Supplemental New Drug Application (sNDA) dated and received on January 16, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Saxenda (liraglutide [rDNA origin] injection).

We acknowledge receipt of your amendment dated March 18, 2015, containing labeling.

This "Changes Being Effected" supplemental new drug application provides for modification of the Highlights section of the package insert to revise the "Initial U.S. Approval" date from 2014 to 2010.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at

http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Pat Madara, Regulatory Project Manager, at (301) 796-1249.

Sincerely,

{See appended electronic signature page}

James P. Smith, MD, MS
Deputy Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling [Package Insert and MedGuide (not revised)]

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/s/

JAMES P SMITH
03/27/2015

Exhibit R

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*:	FROM *(Name, Office/Division, and Phone Number of Requestor)*:
CDER OSE Consults Millie Wright Mildred.Wright@fda.hhs.gov Office of Safety and Epidemiology WO22 RM4492, phone: 6-1027	John Bishai Ph.D. Regulatory Project Manager DMEP, HFD-510, phone #: 6-1311

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
9/16/2009		21-919	Original Submission	April 5, 2005

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Byetta (exenatide)	Standard	Anti-diabetic agent	October 30, 2009

NAME OF FIRM: Amylin Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☒ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☒ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: Please perform an AERS search for pancreatic cancer and (medullary) thyroid tumors. Specifically, we ask that you pull the cases referenced in the attached report and to provide reporting rates of these cancers relative to other anti-diabetic therapies.

Direct link to edr: \\Cdsesub1\evsprod\NDA021995\021995.enx

Please refer to the Berstein Report which is a report comparing AERS reports for Byetta, Januvia, and other products specifically looking at Adverse Event Database, Real World Tolerability, & Expert Interviews.

The document can be found in the DMEP eRoom:
http://eroom.fda.gov/eRoom/CDER3/CDERDivisionofMetabolismandEndocrinologyProductsConsults/0_f0f0

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one) ☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21919	ORIG-1	AMYLIN PHARMACEUTICALS INC	BYETTA (EXENATIDE) INJECTION

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/s/

JOHN M BISHAI
09/17/2009

Exhibit S

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Office of Surveillance and Epidemiology
Division of Drug Risk Evaluation

Date:	December 10, 2009
To:	Mary Parks, M.D., Director, Division of Metabolism and Endocrinology Products
Through:	Mark Avigan, M.D., C.M., Director Division of Pharmacovigilance 1 Office of Surveillance and Epidemiology (DPV 1)
From:	Allen Brinker, M.D., M.S., Team Leader Division of of Pharmacovigilance 1
Subject:	Pancreatic cancer
Drug Name(s):	Exenatide, sitagliptin, and other anti-diabetics (class)
Application Type/Number:	21-773 (exenatide) 21-995 (sitagliptin) 22-044 (sitagliptin + metformin)
Applicant/sponsor:	N/A
OSE RCM #:	2009-1704

1 INTRODUCTION

In a consult request dated 21 September 2009, the Division of Metabolic and Endocrine Products (DMEP) asked the OSE Division of Pharmacovigilance I (DPV I) to review the Adverse Events Reporting System (AERS) database for cases of pancreatic cancer in association with sitagliptin, exenatide, and other anti-diabetic therapies. In addition DPV I, was asked to assess the relative frequency of this event with these agents (e.g., through calculation of reporting rates).

The interest in this consult request was based on a business report ("Bernstein Research," May 29, 2009) that conducted a datamining analysis of the public version of the AERS database. This report noted an absolute report count of 50 reports of pancreatic cancer in association with exenatide and 12 such reports for sitagliptin. In addition, the analysis noted that these counts represented 21% and 40%, respectively, of all cancer reports for these two agents. This frequency (or disproportionality) was assessed as higher in comparison to other anti-diabetic agents. No further discussion of any possible safety signal for pancreatic cancer in association with these two agents is advanced in the report.

2 METHODS AND MATERIAL

This consult request includes both a search of the AERS database and a literature review using the NIH PubMed database of publications. The AERS database was searched in order to 1) rank cancers reported in association with popular and systemically active anti-diabetic therapies included in this review and 2) enumerate and retrieve domestic (US) reports of pancreatic cancer associated with these agents (see Table 1 for list of agents).

From a practical standpoint, spontaneous reports may offer insight into drug-associated cancers when then cancer of interest is rare in the background population.[1,2] As advanced by the National Cancer Institute (NCI)[3], "rare" have been somewhat arbitrarily characterized as those with incidence of less than 35,000 new cases per year for all ages. Generally, it is difficult to derive from spontaneous adverse event reports an inference for causality for cancers which are relatively common in the population. However, the identification of a cluster of very rare cancers in association with exposure to a specific product may signal a potential drug-related event. A table included in the addendum lists estimated new cancer cases and deaths by sex in the United States for 2009.[4] As shown in this table, the incidence of pancreatic cancer of all forms in 2009 is

estimated to be 42,470. This would place it in the "not rare" category, with limited inference to be offered from an analysis of spontaneous reports for causal association. However, DPV I has chosen to undertake this review given reports of pancreatitis and ensuing regulatory action on exenatide and sitagliptin.[5,6]

Based on any cases recovered in this review, because of secular reporting trends it would not be possible to compare reporting rates across the class of anti-diabetics included in this review due to the large difference in time since initial marketing. Such drug-against drug reporting rate comparisons are typically valid for products that were initially marketed within 2-3 years of each other and used in very similar treatment populations. Moreover, because pancreatic cancer is deemed as not rare, the inference from any such comparison would be problematic.

2.1 Data sources and search criteria

- Search date: 3 November 2009
- Drug names: anti-diabetics (see Table 1)
- MedDRA search term(s):
    - Cancer ranking

      Custom search based on HLTs for all malignant neoplasms
    - Enumeration and retrieval of reports

      Pancreatic neoplasms malignant (excluding islet cell and carcinoid) [HLT]

2.2 Literature search

The NIH PubMed database was search on November 12, 2009 using the strings of "pancreas," or "pancreatic," and "cancer," or "neoplasm," and "diabetes," or "diabetic." A second search was undertaken using one of the drug names appearing in Table 1 along with of "pancreas," or "pancreatic," and "cancer," or "neoplasm."

3 RESULTS

3.1 Absolute frequency

The frequency of domestic (US) reports of pancreatic cancer reported in association with the selected anti-diabetic agents from a review of the AERS database is shown in Table 1 (column 1).

Table 1. Crude (unreviewed) domestic report counts (column 1) and reviewed cases of pancreatic cancer (column 2) reported in association with selected anti-diabetics as retrieved from the AERS database.

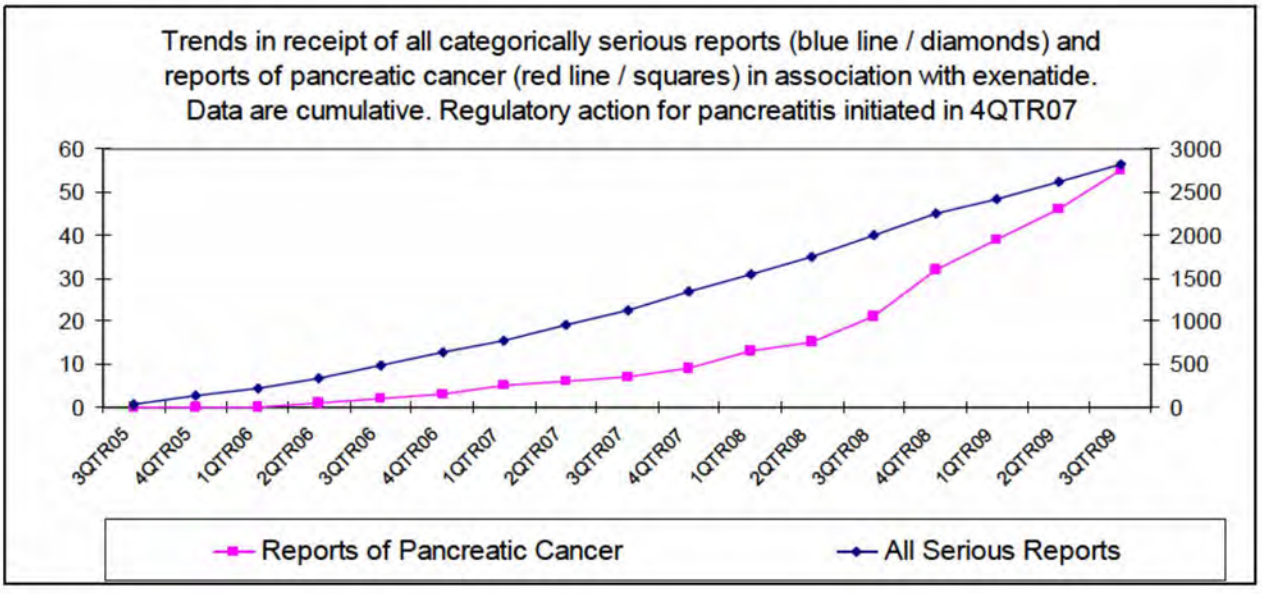
	Crude (unreviewed) report counts*	Reviewed and unduplicated cases
Exenatide	56	46
Sitagliptin**	11	10
Pramlintide	1	1
Nateglinide	0	0
Repaglinide	0	0
Pioglitazone**	21	16
Rosiglitazone**	10	8
Glimepiride**	1	0
Glipizide**	5	3
Glyburide**	1	0
Metformin	11	8

*may include duplicate reports

**includes single and combination products (e.g., in combination with metformin)

With interest in the number of reports for exenatide and the potential effect of regulatory action on reporting for exenatide, cumulative reporting for pancreatic cancer is shown in the figure on the following page. For reference, reporting for any serious event reported in association with exenatide is also provided. Examination of the figure suggests that reporting of pancreatic cancer as a function of time increased following regulatory action in 4QTR07. A slight increase in reporting appears in 1QTR08; this becomes more defined in 4QTR08 and remains through the end of the time period under review (3QTR09). In contrast, no notable change in the slope for reporting of categorically serious events is appreciated. Although it is subject to conjecture, the change in slope for pancreatic cancer in contrast to all serious reporting is consistent with a phase of stimulated reporting for this event. An increase in reporting of pancreatitis in association with

exenatide in close temporal association with regulatory activities (4QTR07) was described in a previous review.[7]



3.2 Within drug ranking

For each product included in this review, the frequency of domestic reports of malignancies were ranked by order of appearance (top five). These data are shown in Table 2 placed at the end of document. Based on the threshold of top 5, *hepatic neoplasm malignant* and *pancreatic carcinoma* are the most frequently reported malignancies, appearing in 6 of the 9 agents (including one "class" consisting of 3 agents) for each malignancy. Each malignancy also represented the most frequent appearing malignancy for 3 agents or the agents grouped as a class. The second most frequently appearing malignancies were *bladder cancer* (n=5) and *colon + gastrointestinal cancer* (n=5).

3.3 Adjudication for case series

The 117 domestic reports identified in the search of the AERS database were recovered and subjected to hands-on review. Reports were reviewed to certify drug exposure and a new diagnosis of pancreatic cancer while on therapy with one of the selected agents. Duplicate reports, study reports, and hearsay reports were excluded. Reports that included metforim as combination therapy (e.g., Avandamet) or in combination were assigned to the other agent (e.g., rosiglitazone). Thus, cases for metformin indicate apparent monotherapy. Case counts are shown in Table 1,

column 2. Age, sex, state, pancreatitis at time of diagnosis, and time-to-onset (or latency) were collected from each case. Aggregated data from these case series are shown in Table 3.

Table 3. Attributes compiled from review of spontaneous cases (as case series) of pancreatic cancer reported in association with selected anti-diabetic agents.

Agent	Total Cases in series	Age – years median	Gender distribution (M/F/NS)	Concurrent diagnosis of pancreatitis at time of cancer diagnosis	Time (months) from initiation of treatment to cancer diagnosis median
exenatide	46	65.5	24 / 21 / 1	4 (9%)	10
pioglitazone	16	73	9 / 7 / 0	1 (6%)	1
sitagliptin	10	62	4 / 6 / 0	1 (10%)	2
rosiglitazone	8	64.5	5 / 1 / 2	0	7.5
metformin	8	65	4 / 4 / 0	0	6
sulfonylurea*	3	72	2 / 1 / 0	0	24
pramlintide	1	79	1 / 0/ 0	0	12

*represents 3 cases for glipizide

As shown in Table 3, there are differences in the median latency between agents: 10 months and 7.5 months for exenatide and rosiglitazone versus 1 month and 2 months for pioglitazone.

3.4 Literature search

The search of the NIH PubMed database (November 2009) resulted in identification of numerous studies based on the search criteria described above. This was not unexpected as obesity, which can predispose to type 2 diabetes mellitus (DM2) – along with cigarette smoking and family history - are well recognized risk factors for pancreatic cancer.[8] Because of the breadth of the potential material, two very recent and relevant articles were chosen for inclusion and discussion. These articles, one study[9] and the accompanying editorial[10], were published in ***Gastroenterology*** in August 2009 and are focused on the potential differential risk for pancreatic cancer between anti-diabetic agents. The study report[9] by Li et al describes a hospital-based case-control study. The study, based in the University of Texas M.D. Anderson Cancer Center, includes 973

pathologically confirmed cases of pancreatic ductal adenocarcinoma and 863 controls. In a finding consistent with previous studies, Li et al reported that a diagnosis or treatment for DM2 was a strong risk factor for a ductal adenocarcinoma (frequency of DM2 in cases = 26.6%; frequency in controls = 12.6%: OR=2.5). With interest in medication exposure, ever users of metformin with a duration of DM2 of > 2 years had a significantly lower likelihood of pancreatic cancer compared to those who had not taken metformin (OR 0.41; 95% CI 0.19-0.87). In contrast, users of insulin demonstrated an elevated likelihood for pancreatic cancer (OR 5.0; 95% CI 2.4-10.7)) in comparison to never users as were recipients of insulin secretagogues (OR=1.7; NS) or thiazolidinediones [TZDs] (OR=1.65; NS), again with restriction to those individuals with a duration of DM2 of > 2 years.

In the accompanying editorial[10], Yang further advances a mechanism to outline differential risk for pancreatic cancer – and cancers of any type – based on pharmacologic effects of anti-diabetic therapy. Principle among these mechanisms is the effect of hyperinsulinemia – either stimulated (i.e., through use of a secretagogue) or exogenous (i.e., insulin injection). To this point metformin's principal action is to increase sensitivity of peripheral tissues to endogenous insulin and thus reduce the hyperinsulinemic state of DM2. Although TZDs share this attribute, the study reported a point estimate suggestive of increased likelihood for pancreatic cancer with ever use of a TZD. As products, both exenatide and sitagliptin were too new to be observed in the case-control study by Li et al. Nonetheless, their mechanism of action includes increases insulin secretion and thus, it seems reasonable that they would more closely resemble the TZDs in effects on insulin resistance and insulin serum concentration in contrast to the primary effects of metformin.

Apparent differences in likelihood (or risk) for pancreatic cancer with exposure to different antidiabetic therapies could also be confounded by timing when different products during the course of DM2 are typically used to treat patients: metformin as first line therapy, followed by secretagogues, followed by insulin. Under the assumption that diabetes is a risk factor for pancreatic cancer and duration of diabetes increases risk, then apparent differences in risk for pancreatic cancer between different products could be affected by the order of treatments in a standard treatment paradigm.

4 DISCUSSION AND CONCLUSION

Cases of pancreatic cancer have been reported with all the agent subclasses (incretin, TZD, sulfonylurea, metaglinide) included in this review. Based on an assessment that pancreatic cancer is a relatively common cancer in the adult population, little inference for risk is appreciated from review of spontaneous reports of pancreatic cancer in adult recipients of anti-diabetics agents. Therefore, a reporting rate analysis has not been undertaken. With this baseline, more reports of pancreatic cancer were observed for exenatide in comparison to other agents, including sitagliptin. This could be attributed to notoriety following regulatory action for edematous pancreatitis in association with exenatide. There is also a noteworthy difference in time-to-diagnosis (or latency) of 10 months (exenatide) versus 2 months (sitagliptin) between these agents. However, there is also a notable difference in latency of 7.5 months (rosiglitazone) and 1 month (pioglitazone) for the two TZDs. Such variability - even between very similar products - suggests the possibility that these differences may not reflect true differences in product specific risk for pancreatic cancer.

A review of the literature notes that obesity, a strong risk factor for DM2, is also considered a risk factor for pancreatic cancer. Thus, any association between specific treatments for DM2 and pancreatic cancer could be spurious and the result of confounding due to a primary association with DM2. However, a recent study controlled for duration of disease suggests that treatment with metformin is associated with a decreased likelihood for pancreatic cancer. Therefore, a role for anti-diabetic agents in the development of pancreatic cancer or a differential risk between agents cannot altogether be excluded.

5 CONCLUSIONS AND RECOMMENDATIONS

- Spontaneous reports of pancreatic cancer have been received for most of the anti-diabetic agents included in this review. Pancreatic cancer is one of the most frequent cancers to appear in spontaneous adverse event reporting for this therapeutic class. However, a causal association between exposure to one of these agents and pancreatic cancer is indeterminate at this time.
- Based on a review of the literature, treatment with metformin in patients without contraindications and as advanced by consensus treatment recommendations for initial drug treatment of DM2 could be associated with a reduced likelihood for cancer, including pancreatic cancer. Differential cancer frequency might be observable in active-controlled trials of long duration and that randomize exposure to metformin.
- DPV I will continue to monitor for is event in this group of products.
- No labeling recommendations are offered.

6 REFERENCES

1. Memorandum dated 13 November 2009. Joslyn Swann to Mary Parks. Malignancies in association with insulin glargine (Lantus).
2. Memorandum dated 3 December 2009. Allen Brinker to Mary Parks. Medullary thyroid cancer in association with exenatide, sitagliptin, and other anti-diabetic agents.
3. Common Cancer Types. National Cancer Institute. Available at: http://www.cancer.gov/cancertopics/commoncancers. Accessed: September 2009.
4. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer Statistics 2009. CA Cancer J Clin 2009;59(4):225-49.
5. Memorandum dated July 12, 2007. Joslyn Swann to Mary Parks. Drug-induced pancreatitis in association with exenatide.
6. Memorandum dated June 19, 2009. Yinghua Wang and Syed R. Ahmad to Mary Parks. Acute pancreatitis and necrotizing pancreatitis in association with sitagliptin (Januvia) and sitagliptin / metformin (Janumet).
7. Memorandum dated June 19, 2009. Allen Brinker to Mary Parks. Epidemiology Team Leader covering memorandum with alternate epidemiology analysis for joint DPV 1 and DEPI review of acute pancreatitis in association with sitagliptin.
8. Wynder EL, Mabuchi K, Maruchi N, Fortner JG. Epidemiology of cancer of the pancreas. J Natl Cancer Inst 1973;50(3):645-67.
9. Li D, Yeung SC, Hassan MM, Konopleva M, Abbruzzese JL. Antidiabetic therapies affect risk of pancreatic cancer. Gastroenterology 2009;137(2):482-8.
10. Yang YX. Do diabetes drugs modify the risk of pancreatic cancer? Gastroenterology 2009;137(2):412-5.

Table 2. Total and rank order of malignancies for popular anti-diabetic agents based on domestic (US) reports in AERS database as of November 16, 2009.									
Agent	**Exenatide**	**Pioglitazone**	**Glipizide**	**Metformin**	**Rosiglitazone**	**Glyburide**	**Sitagliptin**	**Meglitinides**	**Glimepiride**
Total reports of malignancy	297	150	106	104	103	65	38	20	14
Rank									
1	Pancreatic carcinoma	Pancreatic carcinoma	Breast cancer female	Hepatic neoplasm malignant	Hepatic neoplasm malignant	Neoplasm malignant	Pancreatic carcinoma	Lung neoplasm	Hepatic neoplasm malignant
2	Breast cancer	Bladder cancer	Neoplasm malignant	Pancreatic carcinoma	Neoplasm malignant	Gastro-intestinal cancer	Hepatic neoplasm malignant	Breast cancer	Bladder cancer
3	Neoplasm malignant	Colon cancer	Colon cancer	Neoplasm malignant	Pancreatic carcinoma	Hepatic neoplasm malignant	Leukaemia	Leukaemia*	Breast cancer
4	Thyroid neoplasm	Hepatic neoplasm malignant	Gastro-intestinal cancer	Bladder cancer	Bile Duct Cancer	Lung neoplasm malignant	Lung neoplasm malignant	Pancreatic carcinoma*	Gastro-intestinal cancer
5	Uterine cancer	Lung neoplasm malignant	Lung neoplasm malignant	Gastro-intestinal cancer	Bladder cancer	Bladder cancer	Lymphoma	Bladder cancer*	Lymphoma

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21773	ORIG-1	AMYLIN PHARMACEUTICALS INC	BYETTA (EXENATIDE) INJ,SOL 0.25MG/ML
NDA-21995	ORIG-1	MERCK CO INC	JANUVIA 100MG (SITAGLIPTIN PHOSPHATE)
NDA-22044	ORIG-1	MERCK AND CO INC	JANUMET(PHOSPHATE/METFORMIN HCL FIXED DO

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/s/

ALLEN D BRINKER
12/10/2009

MARK I AVIGAN
12/10/2009

Exhibit T

Drugs

FDA Drug Safety Communication: FDA investigating reports of possible increased risk of pancreatitis and pre-cancerous findings of the pancreas from incretin mimetic drugs for type 2 diabetes

en Español[1]

[3-14-2013] The U.S. Food and Drug Administration (FDA) is evaluating unpublished new findings by a group of academic researchers that suggest an increased risk of pancreatitis, or inflammation of the pancreas, and pre-cancerous cellular changes called pancreatic duct metaplasia in patients with type 2 diabetes treated with a class of drugs called incretin mimetics. These findings were based on examination of a small number of pancreatic tissue specimens taken from patients after they died from unspecified causes. FDA has asked the researchers to provide the methodology used to collect and study these specimens and to provide the tissue samples so the Agency can further investigate potential pancreatic toxicity associated with the incretin mimetics.

Drugs in the incretin mimetic class include exenatide (Byetta, Bydureon), liraglutide (Victoza), sitagliptin (Januvia, Janumet, Janumet XR, Juvisync), saxagliptin (Onglyza, Kombiglyze XR), alogliptin (Nesina, Kazano, Oseni), and linagliptin (Tradjenta, Jentadueto). These drugs work by mimicking the incretin hormones that the body usually produces naturally to stimulate the release of insulin in response to a meal. They are used along with diet and exercise to lower blood sugar in adults with type 2 diabetes.

FDA has not reached any new conclusions about safety risks with incretin mimetic drugs. This early communication is intended only to inform the public and health care professionals that the Agency intends to obtain and evaluate this new information. FDA will communicate its final conclusions and recommendations when its review is complete or when the Agency has additional information to report.

FDA previously warned the public about postmarketing reports of acute pancreatitis, including fatal and serious nonfatal cases, associated with the use of the incretin mimetic drugs exenatide[2] and sitagliptin[3]. A recently published study that examined insurance records also found the use of exenatide or sitagliptin could double the risk of developing acute pancreatitis.[1] The *Warnings and Precautions* section of the drug labels and the patient Medication Guides for incretin mimetics contain warnings about the risk of acute pancreatitis. FDA has not previously communicated about the potential risk of pre-cancerous findings of the pancreas with incretin mimetics. Further, FDA has not concluded these drugs may cause or contribute to the development of pancreatic cancer.

At this time, patients should continue to take their medicine as directed until they talk to their health care professional, and health care professionals should continue to follow the prescribing recommendations in the drug labels.

FDA is continuing to evaluate all available data to further understand this potential safety issue. In addition, FDA will participate in the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and National Cancer Institute's (NCI) Workshop on Pancreatitis-Diabetes-Pancreatic Cancer in June 2013[4] to gather and share additional information.

FDA urges both patients and health care professionals to report adverse events involving incretin mimetics to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.

Reference

1. Singh S, Chang HY, Richards TM, Weiner JP, Clark JM, Segal JB. Glucagonlike peptide 1-based therapies and risk of hospitalization for acute pancreatitis in type 2 diabetes mellitus: a population-based matched case-control study. JAMA Intern Med 2013 Feb 25:1-6. doi: 10.1001/jamainternmed.2013.2720. [Epub ahead of print].

Related Information

- Information for Healthcare Professionals: Exenatide (marketed as Byetta) - 8/2008 Update[5] [ARCHIVED]
- Information for Healthcare Professionals - Acute pancreatitis and sitagliptin (marketed as Januvia and Janumet)[6] [ARCHIVED]
- FDA Drug Safety Podcast: FDA investigating reports of possible increased risk of pancreatitis and pre-cancerous findings of the pancreas from incretin mimetic drugs for type 2 diabetes[7]

Contact FDA
1-800-332-1088
1-800-FDA-0178 Fax
Report a Serious Problem

MedWatch Online[8]

Regular Mail: Use postage-paid FDA Form 3500[9]
Mail to: MedWatch 5600 Fishers Lane
Rockville, MD 20857

Page Last Updated: 03/18/2013
Note: If you need help accessing information in different file formats, see Instructions for Downloading Viewers and Players.

Links on this page:

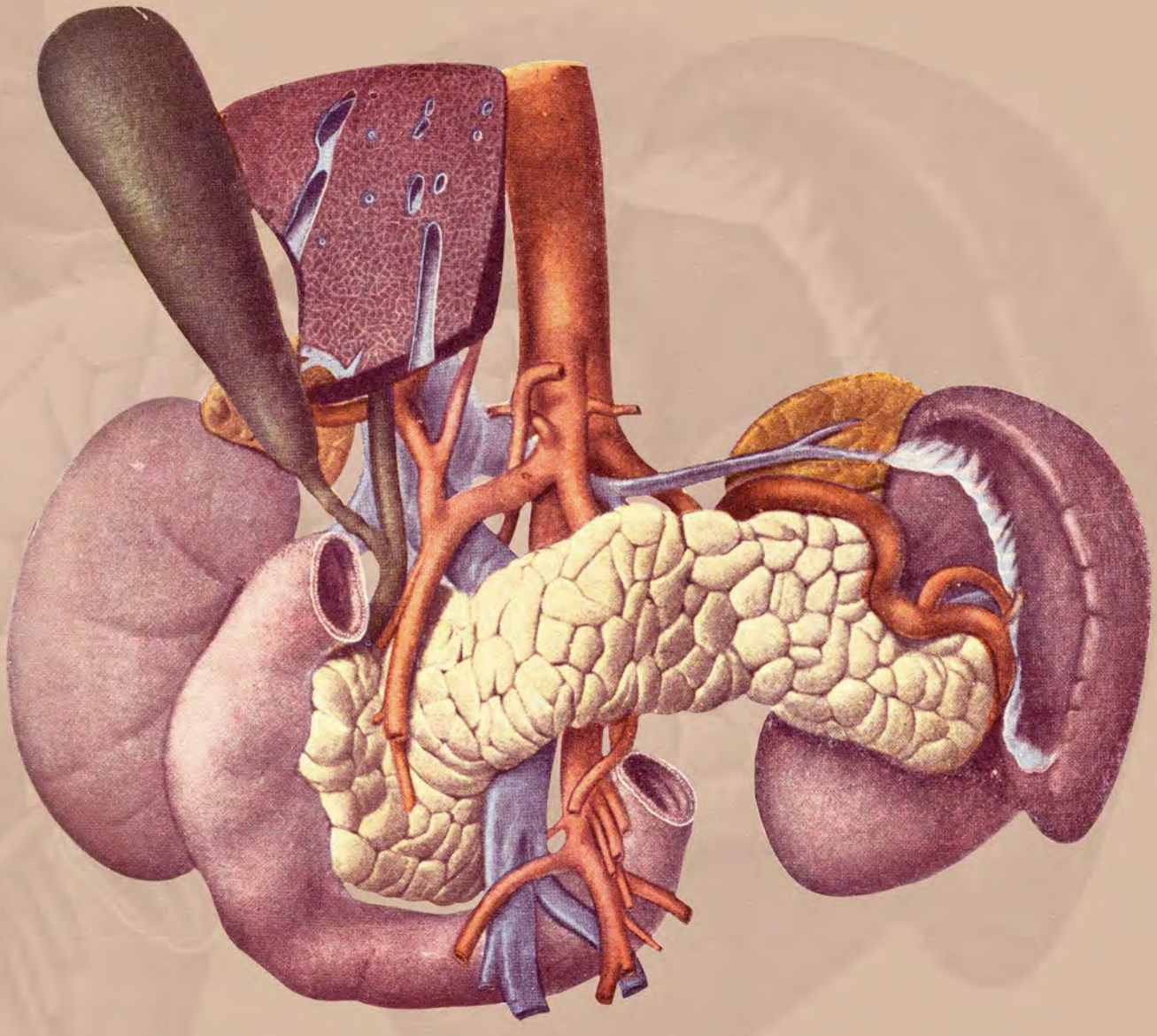
1. /Drugs/DrugSafety/ucm344280.htm
2. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124713.htm
3. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm1
4. http://www2.niddk.nih.gov/News/Calendar/PDPC2013
5. /Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124713.htm
6. /Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm183764.htm

7. /Drugs/DrugSafety/DrugSafetyPodcasts/ucm344232.htm
8. https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm
9. http://www.fda.gov/downloads/Safety/MedWatch/DownloadForms/UCM082725.pdf

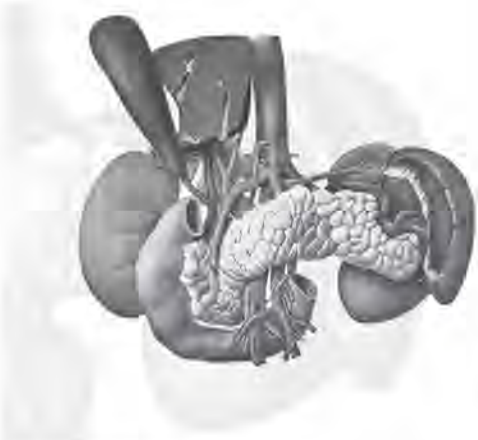
Exhibit U

June 12 - 13, 2013

Pancreatitis
Diabetes
Pancreatic Cancer
Workshop



Lister Hill Auditorium
NIH Campus, Bethesda, MD



FDA Surveillance of Adverse Drug Effects

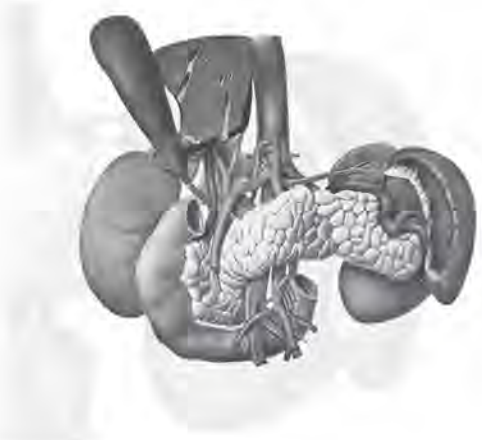
B. Timothy Hummer, Ph.D., D.A.B.T.

Division of Metabolism and Endocrinology Products, Center for Drug Evaluation and Research, U.S. Food and Drug Administration

Published reports of pancreatic injury in animals exposed to GLP-1-based therapeutics, which include dipeptidyl peptidase 4 inhibitors (DPP4i) and GLP-1 analogues, has contributed, in part, to safety concerns of using approved GLP-1-based therapies as a chronic treatment in the Type 2 diabetic (T2D) population. Investigational drugs are subjected to extensive non-clinical testing, including 6- to 9-month studies in rodents and non-rodents, and 2-year evaluation of carcinogenicity in rats and mice. Overt pancreatic toxicity or pancreatic neoplasms have not been observed across the DPP4i or GLP-1 analogue drug classes in these studies that would indicate a risk to human safety. However, upon the discovery of this potential safety signal, the data from chronic toxicology and carcinogenicity studies, as available, were re-examined across approximately 50 investigational GLP-1-based therapeutics to ascertain whether subtle histological changes were present that might indicate pancreatic injury. Background histological changes in control animals, notably acinar and islet hyperplasia/hypertrophy, inflammation, and acinar atrophy, were generally of low incidence and minimal severity. Few drugs altered these background findings, and those that did resulted in minimal increases in either incidence or severity, typically only at the highest dose evaluated, which is several-fold higher than the human therapeutic dose.

Regulatory toxicology studies are conducted in healthy, normoglycemic rodents and non-rodents. It is reasonable to suggest that GLP-1-based therapeutics exert adverse effects on the exocrine pancreas under pathophysiological conditions that predispose to pancreatitis, such as the metabolic abnormalities present in T2D. The FDA therefore issued a post-marketing requirement (PMR) on the sponsors of exenatide, liraglutide, and sitagliptin to conduct a pancreatic toxicology study in a rodent model of T2D. These studies were required to be at least 3-months' duration in a model marked by high blood glucose and triglycerides, to include extensive histological assessment of the endocrine and exocrine pancreas with ductal structures, and include proliferative staining of pancreatic exocrine/endocrine tissues. Three studies that met the criteria of the PMR have been submitted to the FDA for review. While effects of treatment were noted on endocrine structures (e.g., islet hypertrophy/greater mass), none of the three studies definitively demonstrated a treatment-related adverse effect on exocrine histology or proliferation. FDA veterinary pathologists that re-examined the histological slides from one of these studies similarly concluded that a definitive toxicological effect was not evident; however, it was commented that exacerbation of background histological changes, which was seen sporadically and minimally with treatment (e.g., peri-ductal inflammation, islet degeneration, intraluminal concretions), could be interpreted as representing an exacerbation of pancreatic injury, albeit with uncertain relevance to patients with T2D.

The FDA also initiated research into identifying an experimental model that would enable a comparative toxicological assessment of potential pancreatic toxicity for investigational GLP-1-based therapies currently under development. Chemically induced models of pancreatic injury, Zucker Diabetic Fatty rats, and mice fed a standard



FDA Surveillance of Adverse Drug Effects

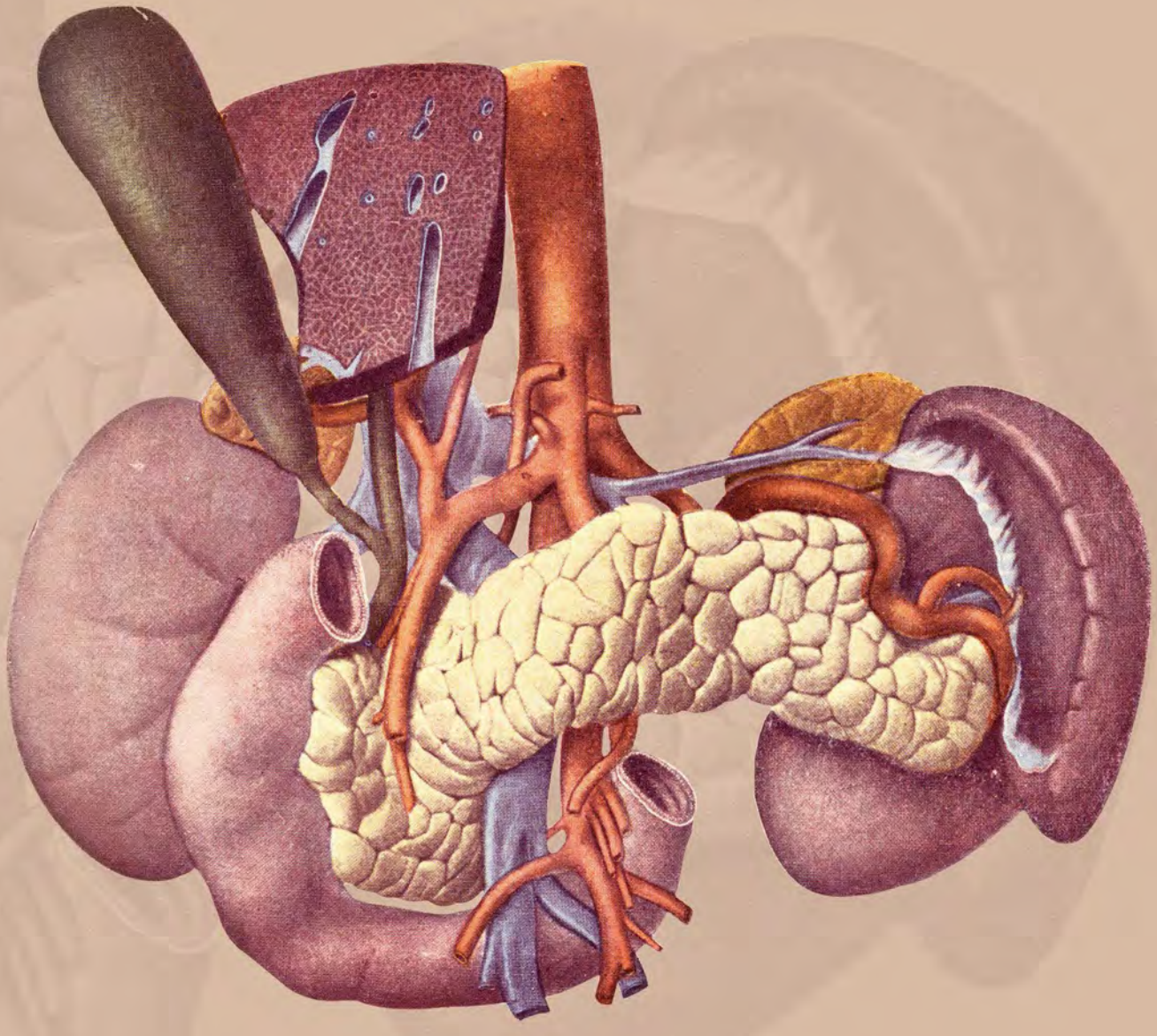
(Continued)

or high-fat diet have thus far been investigated. Among these models, mice fed a high-fat diet and administered exenatide displayed a time- and dose-dependent exacerbation of acinar cell hyperplasia, atrophy, fibrosis, and increased peri-ductal inflammation. The effect of exenatide was multi-focal and associated with histological changes of minimal to moderate severity. These changes were not associated with animal morbidity or mortality. Assessing the clinical significance of these findings and the potential utility of the murine model for regulatory toxicology testing is an ongoing effort. The FDA has continuously monitored the GLP-1-based therapies since initial approval of these two drug classes. Continued non-clinical investigation remains an important component of the FDA's efforts to clarify the potential pancreatic toxicity of the GLP-1-based therapies and to aid in the evaluation of compounds currently under development.

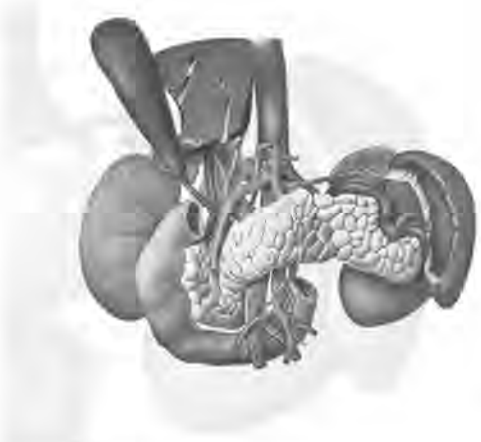
Exhibit V

June 12 - 13, 2013

Pancreatitis
Diabetes
Pancreatic Cancer
Workshop



Lister Hill Auditorium
NIH Campus, Bethesda, MD



FDA's Approach to Addressing a Pancreatic Safety Signal With Incretin Mimetics: Pharmacovigilance and Pharmacoepidemiology

Solomon Iyasu, M.D., M.P.H.

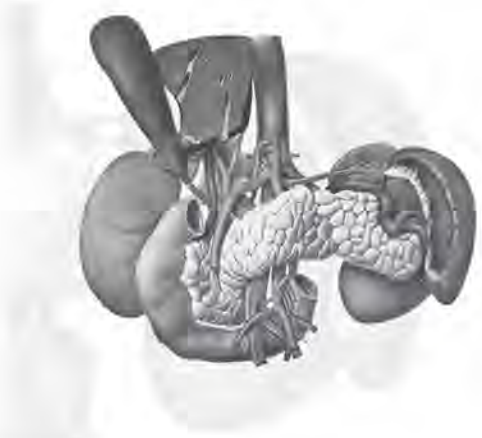
U.S. Food and Drug Administration, Silver Spring, MD

Cases of acute pancreatitis (AP), including necrotizing and hemorrhagic types in association with GLP-1 incretin mimetic drug treatment of patients with Type 2 diabetes, have been reported to FDA's Adverse Event Reporting System (AERS) in the postmarketing setting. The safety of GLP-1-based therapies, including potential pancreatic toxicity related to AP, have been continuously monitored soon after approval of exenatide, the first drug approved in the class. These concerns have been the subject of multiple FDA reviews, labeling changes, and FDA communications. Additionally, external researchers published data mining analyses of the publicly available AERS data (Elashoff, *Gastroenterology* 2011;141:150. Quarterwatch 2013) and have raised concerns regarding the risk of AP and pancreatic and thyroid cancer in association with GLP-1-based drug therapies. The limitations of AERS data (under-reporting of events due to the voluntary nature of reports, lack of an accurate population denominator, and inadequate documentation of the clinical details, including the presence of comorbidities, concomitant medications, and important risk factors) do not allow one to calculate incidence rates, establish a causal association between the drug and the adverse event, or to estimate the magnitude of the association or determine any differences in risk for pancreatic toxicity among GLP-1 agents. Interpretation of AERS data is limited by the lack of an adequate control data and evidence that suggests a possible increased background risk in the indicated patient population. AERS data mining signals, such as for pancreatitis and pancreatic and thyroid cancers reported in the literature and FDA's own reviews utilizing similar methods for GLP-agents and other drug therapies, are considered to be hypothesis generating and cannot be used to establish or refute a drug effect.

FDA has issued safety communications and added labeling to the Warnings and Precautions section of all GLP-1 based drugs warning prescribers and patients about post-marketing reports of fatal and non-fatal cases of AP. Information also has been added in the Important Limitations of Use subsection of the Indications and Usage Section, the Adverse Reactions, Postmarketing subsection, and the Patient Counseling Information Section of the labeling in addition to requiring patient labeling (a Medication Guide) to warn patients of the risk of acute pancreatitis. FDA has required the manufacturers to conduct epidemiological studies of pancreatic toxicity safety signals in order to confirm and quantify the potential association with GLP-1 therapies in Type 2 diabetics.

FDA has required that cases of pancreatitis and pancreatic cancer be reported as adverse events of special interest in large cardiovascular outcome trials that are required for the GLP-1 based therapies. The signal for medullary thyroid cancer, a rare form of thyroid cancer that has been observed in animal studies with long-acting GLP-1 agonists, is labeled in a Boxed Warning in all approved long-acting GLP-1 agonists (Victoza and Bydureon), and FDA has required that all manufacturers of approved GLP-1 agonists participate in a Medullary Thyroid Cancer Registry as a postmarketing requirement. The clinical relevance of this animal finding remains unknown.

Review of the FDA-required epidemiological studies submitted to the Agency and the published epidemiological literature have provided conflicting results and do not provide reliable evidence to refute or support a causal link between GLP-1-based therapies and the risk of AP. Six observational studies investigated the risk of acute pancreatitis associated with GLP-1-based therapies (exenatide or sitagliptin). Among them, one study detected an increased risk with recent or past, but not current, use (Dore, *Diabetes Obes Metab* 2011;13:559), and one study



FDA's Approach to Addressing a Pancreatic Safety Signal With Incretin Mimetics: Pharmacovigilance and Pharmacoepidemiology

(Continued)

found an increased risk for acute pancreatitis with current and recent use (Singh, *JAMA Intern Med* 2013;173:534). No increase in risk was found in the remaining four studies (Dore, *Curr Med Res Opin* 2009;25:1019. Garg, *Diabetes Care* 2010;33:2349. Romley, *Diabetes Technol Ther* 2012;14:904. Wenten, *Diabet Med* 2012;29:1412). Serious methodological shortcomings shared by the studies, including lack of outcome validation and incomplete covariate adjustment, preclude conclusive results.

FDA's AERS data are useful in identifying potential drug-related serious safety signals, particularly events that have a low background rate in the population but are less suitable for detecting relatively more common events and events with long latency periods, such as pancreatitis, pancreatic cancer, and thyroid cancer. Additional data mining analysis of AERS is unlikely to shed more light on these safety signals. Evaluation of the potential association between GLP-1-based therapies and pancreatitis and pancreatic and thyroid cancers will require adequately powered, long-term epidemiological studies.

Exhibit W

CORRECTIONS

Brief Report: Transferable Vancomycin Resistance in a Community-Associated MRSA Lineage (April 17, 2014;370:1524-31). In Figure 3A (page 1529), the clone listed as "Chilean/USA500" should have been "Chilean/Cordobes." The article is correct at NEJM.org.

Case 9-2014: A 34-Year-Old Woman with Increasing Dyspnea (March 20, 2014;370:1149-57). Video 2, which focused on the pulmonary valve, was not the correct video and did not correspond to the legend, which described the left ventricle. The video has been replaced and the article is correct at NEJM.org.

Pancreatic Safety of Incretin-Based Drugs — FDA and EMA Assessment (February 27, 2014;370:794-7). In the second paragraph (page 794), the second sentence should have described incretins as "intestinal hormones that regulate the postprandial production of insulin and glucagon by the pancreas," rather than ". . . intestinal hormones that stimulate. . . ." The article is correct at NEJM.org.

NOTICES

Notices submitted for publication should contain a mailing address and telephone number of a contact person or department. We regret that we are unable to publish all notices received. Notices also appear on the Journal's website (NEJM.org/medical-conference). The listings can be viewed in their entirety or filtered by specialty, location, or month.

SOCIETY OF LAPAROENDOSCOPIC SURGEONS

The following meeting will be held: "Minimally Invasive Surgery Week 2014: Annual Meeting and Endo Expo" (Las Vegas, Sept. 10–13).

Contact the Society of Laparoendoscopic Surgeons, 7330 SW 62nd Place, Suite 410, Miami, FL 33143; or call (305) 665-9959; or fax (305) 667-4123; or see http://www.sls.org.

IDWEEK 2014

The meeting, entitled "Advancing Science, Improving Care," will be held in Philadelphia, Oct. 8–12.

Contact the Infectious Diseases Society of America, 1300 Wilson Blvd., #300, Arlington, VA 22209; or call (703) 740-4789; or fax (866) 579-0939; or e-mail djohnston@idsociety.org; or see http://www.idweek.org.

UNIVERSITY OF MINNESOTA COLON & RECTAL SURGERY PRINCIPLES COURSE

The course will be offered in Minneapolis, Oct. 8–11.

Contact Mary Pat McGlynn, Minnesota Colon & Rectal Foundation, 5353 Wayzata Blvd., Suite 350, Minneapolis, MN 55416; or call (952) 564-3062; or e-mail info@colonrectalcourse.org; or see http://www.colonrectalcourse.org.

IASGO 2014

The "24th World Congress of the International Association of Surgeons, Gastroenterologists and Oncologists" will be held in Vienna, Dec. 3–6.

Contact ÄRZTEZENTRALE MED.INFO, Helferstorferstrasse 4, P.O. Box 155, 1014 Vienna, Austria; or call (43) 1 531 16-38; or fax (43) 1 531 16-61; or e-mail azmedinfo@media.co.at; or see http://www.iasgo2014.org/.

CHEMOTHERAPY FOUNDATION SYMPOSIUM: INNOVATIVE CANCER THERAPY FOR TOMORROW

The symposium will be held in New York, Nov. 5–7. It is jointly presented by the Icahn School of Medicine at Mount Sinai and the Chemotherapy Foundation.

Contact the Mount Sinai Medical Center, 1 Gustave L. Levy Place, Box 1193, New York , NY 10029; or call (212) 866-2813; or fax (646) 215-7589; or e-mail jaclyn.silverman@mssm.edu; or see http://www.chemotherapyfoundationsymposium.org/CMS/.

PEDIATRIC CLINICAL HYPNOSIS WORKSHOPS

The workshops, available at introductory, intermediate, and advanced levels, will be offered in Minneapolis, Sept. 11–13. They are presented by the National Pediatric Hypnosis Training Institute and co-sponsored by the University of Minnesota Department of Pediatrics and the Minnesota Society of Clinical Hypnosis.

Contact the Office of CME, University of Minnesota, University Park Plaza, Suite 901, 2829 University Ave. SE, Minneapolis, MN 55414; or call (612) 626-7600; or see http://www.nphti.org or http://www.cmecourses.umn.edu.

BIG 4 CANCER CONFERENCE: DETECTION, DIAGNOSIS, TREATMENT, SURVIVORSHIP

The conference will be held in Knoxville, TN, Oct. 24 and 25. It is jointly presented by the University of Tennessee Medical Center Cancer Institute and the University of Tennessee Graduate School of Medicine.

Contact the UT Graduate School of Medicine, UT Medical Center, 1924 Alcoa Highway, Box U-94, Knoxville, TN 37920; or call (865) 974-0280; or fax (865) 974-0264; or see http://www.tennessee.edu/cme/Big4.

MAYO CLINIC

The following courses will be offered in Rochester, MN, unless otherwise indicated: "Controversies in Women's Health" (Chicago, June 12–14); "Mayo Clinic Internal Medicine Board Review" (June 16–20); "Mayo Clinic Radioactive Seed Localized Breast Surgery Workshop" (July 18); "Mayo Clinic Oncology Review" (Minneapolis, July 26); "Mucha Symposium: Meeting the Needs of the Acute Care Surgery and Injured Patient" (Aug. 7 and 8); "Professionalism Today and Tomorrow: Sustaining Trust in a Technology-Driven Health Care World" (Aug. 18 and 19); "6th Mayo Clinic Angiogenesis and Tumor Microenvironment Symposium: from Basic Science and Clinical Challenges to Patient Care" (Aug. 22–24); "Mayo Clinic Gastroenterology and Hepatology Board Review" (Chicago, Sept. 4–7); "Mayo Clinic Nutrition and Wellness in Health and Disease" (San Francisco, Sept. 18 and 19); and "Pediatric Days 2014" (Chicago, Sept. 29 and 30).

Contact the Mayo School of Continuous Professional Development, 200 First St. SW, Rochester, MN 55905; or call (800) 323-2688 or (507) 284-2509; or fax (507) 284-0532; or see http://www.mayo.edu/cme; or e-mail cme@mayo.edu.

AMERICAN SOCIETY OF TROPICAL MEDICINE AND HYGIENE

The "63rd Annual Meeting" will be held in New Orleans, Nov. 2–6.

Contact the American Society of Tropical Medicine and Hygiene, 111 Deer Lake Rd., Suite 100, Deerfield, IL 60015; or call (847) 480-9592; or fax (847) 480-9282; or see http://www.astmh.org.

COMPUTER ASSISTED RADIOLOGY AND SURGERY

The congress will be held in Fukuoka, Japan, June 25–28.

Contact CARS Conference Office, Im Gut 15, 79790 Kuessaberg, Germany; or call (49) 7742-922 434; or fax (49) 7742-922 438; or e-mail office@cars-int.org; or see http://www.cars-int.org.

Exhibit X

About FDA

SMG 2126.3

FDA STAFF MANUAL GUIDES, VOLUME III – GENERAL ADMINISTRATION

EXTERNAL RELATIONS

REVIEW OF FDA-RELATED ARTICLES AND SPEECHES

Effective Date: 02/02/2011

[PDF version[1]]

1. PURPOSE

The purpose of this Staff Manual Guide (SMG) is to provide general procedures for FDA staff to follow when publishing articles or delivering speeches that are FDA related (as defined below in 4A.) whether the articles or speeches are assigned work or outside activities.

2. POLICY

A. FDA encourages employees to share information that may benefit the public health 21 by giving speeches and publishing articles in scientific or professional journals or other publications.

B. If an FDA employee undertakes an FDA-related article or speech that is not part of 25 his or her assigned work (see "Definitions" in section 4.A below), it is considered to be an "outside activity," subject to the requirements for outside activities (see section 7.B.2 below).

C. FDA further encourages employees to consult with their supervisors to determine 30 whether an FDA-related article or speech that is not assigned work, where appropriate in content area, may potentially be conducted as a work assignment.

D. When an article or speech by an FDA employee contains FDA-related material, FDA 34 has an interest in ensuring (1) that nonpublic information (as defined below) is not disclosed and (2) that supervisors within an employee's office or Center have an opportunity to provide feedback on the content of the article or speech for consideration before it is published. If articles or speeches are not part of the employee's assigned work, FDA also has an interest in ensuring that they are not incorrectly construed to represent official FDA determinations, views, or positions.

E. All timeframe references are to **calendar days**.

3. DEFINITIONS

A. Assigned Work. For purposes of the SMG, assigned work is a project that is conducted as part of the employee's official duties. Articles or speeches that flow from assigned work but were not undertaken as part of the employee's official duties are not assigned work.

B. FDA-Related Article or Speech. Any article, poster, abstract, book, book chapter, published writing, presentation, or speech written or presented (or co-written or co-presented) by an FDA employee: (1) that relies on or discusses data or information that was only available to the author

through his or her employment at FDA, or (2) that discusses products or matters within FDA's jurisdiction, or (3) that discusses or analyzes an FDA program, policy, regulation, action or initiative or (4) that could reasonably be perceived to reflect FDA's approach to issues within its jurisdiction.

C. Center(s). One or more of FDA's Office of the Commissioner, Office of Regulatory Affairs, Center for Food Safety and Applied Nutrition, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, Center for Devices and Radiological Health, Center for Veterinary Medicine Center for Tobacco Products, and National Center for Toxicological Research.

D. Employee. Any (1) current employee at FDA or (2) staff fellow at FDA who plans to publish or present an FDA-related article or speech.

E. Supervisor. The FDA employee's direct supervisor or some other official designated by the employee's Center to review FDA-related articles or speeches.

F. Nonpublic information. Information exempt from disclosure under 5 U.S.C. 552 or otherwise protected from disclosure by statute, executive order, or regulation; information that has been designated as confidential by the agency; or information that has not actually been disseminated to the public and is not available to the public upon request (5 CFR 2635.703(b)). Among the laws governing disclosure or requiring confidentiality are the Federal Food, Drug, and Cosmetic Act (e.g., 21 U.S.C. 331(j)), the Freedom of Information Act, the Trade Secrets Act, and the Privacy Act, as well as FDA's implementing regulations (e.g., 21 CFR part 20).

4. BACKGROUND

Section 713 of the Act, which was added by section 1101 of the Food and Drug Administration Amendments Act of 2007, directs FDA to "establish and make publicly available clear written policies to implement [section 713] and govern the timely submission, review, clearance, and disclaimer requirements for articles." An "article" is defined as "a paper, poster, abstract, book, book chapter, or other published writing." Section 713 imposes a 30-day time limit on the agency's review of articles intended for publication. This SMG implements section 713 of the Act but also extends to speeches and other oral presentations.

5. APPLICATION

Centers will implement and follow the general requirements and procedures set forth in this policy. Centers may supplement and expand upon this policy to meet their specific needs through issuance of written standard operating procedures (SOPs), so long as those SOPs do not conflict with the general principles set forth in this SMG. For example, a Center may specify that some designated official other than the employee's supervisor be responsible for conducting the review required by this SMG. Unless supplemented by the SOPs in an employee's Center, however, the policy and procedures set forth in Section 7 of this document apply, as written, to any FDA-related article or speech authored or presented by that employee. If an article or presentation involves multiple FDA employees, all are subject to these procedures.

6. RESPONSIBILITIES AND PROCEDURES

A. FDA-Assigned Articles or Speeches

Articles or speeches that are assigned work will be reviewed and cleared through the standard supervisory channels established by the Center or the agency and on a schedule to be determined by the employee and the supervisor. The time limits given below (in section 7.B.) do not apply to assigned work.

If, during the review and clearance process of an FDA-assigned article or speech, an employee and his or her Center do not agree about the findings, conclusions, or policy implications set forth in the FDA-assigned article or speech, or if the Center determines that the article or speech is not appropriate as an official communication by FDA, the employee may still opt to pursue publishing the article or presenting the speech as a non-assigned FDA-related article or speech providing that he or she follows the procedures in section 7.B below (including use of a disclaimer as required in section 7.B.11).

Even in the case of an FDA-related article or speech that is assigned work, the supervisor and/or the employee may decide to use a disclaimer to emphasize that the views expressed in the article

or speech do not necessarily represent the official views or policies of the agency (*see* 21 CFR 10.85(k)).

B. Non-Assigned but FDA-Related Articles or Speeches

1. An employee must provide any FDA-related article or speech that was not part of the employee's assigned work to his or her supervisor (or other designated official) for review no less than thirty (30) days before pursuing publication of the FDA-related article or presenting the FDA-related speech. This responsibility applies even if the article or speech will not contain the employee's FDA title, affiliation or contact information. In the case of a speech, if the full text of the speech is prepared in advance, it must be submitted to the supervisor. Alternatively, if the full text of the speech is not available, the employee may submit slides or any other written materials that have been prepared in advance of the speech. At a minimum for any speech or other oral presentation (e.g., an appearance on a panel of experts at a conference), the topic to be discussed and an outline of the key points the employee plans to make must be submitted for review. The FDA-related article may not be submitted for publication, nor may the speech or other oral presentation be made, until after the review is completed or the 30-day period for review has expired, whichever occurs first.

2. An employee writing an article or preparing a speech that is not part of his or her assigned work must comply with statutes and regulations that apply to any outside activity. Of note, submission, review and approval of a "Request for Approval of Outside Activity" (form HHS-520) is a separate and distinct requirement from the process under this SMG for reviewing an FDA-related article or speech that was not undertaken as assigned work.[1] Employees should submit any "Request for Approval of Outside Activity" to their supervisor as early as possible.

3. An employee should ensure that the article or speech does not contain any nonpublic information before providing it to the supervisor for review.

4. The employee's supervisor will review the FDA-related article or speech to identify: (1) nonpublic information and (2) potential major concerns regarding the accuracy of the information or the manner in which information is presented.

5. Within the 30 days following submission of the non-assigned FDA-related article or speech, the supervisor must provide in writing any changes the supervisor notes that are necessary to protect nonpublic information. These comments may also include suggested revisions for the employee's consideration with respect to accuracy and the presentation of information. The employee, however, retains the responsibility for both protecting nonpublic information and for the substantive content of the article or speech, including its accuracy.

6. The employee must make any specific changes needed to prevent disclosure of nonpublic information.

7. If the article addresses subjects that ordinarily fall within the purview of other Centers, the employee and supervisor should work together to ensure that those other Centers are identified and have an opportunity to review and provide comments within the 30-day review period, as well.

8. If time and employee resources permit, or if the content raises specific issues, the supervisor (and other employees or Centers, as applicable) may choose to conduct a more detailed evaluation and provide comments regarding the article, e.g., its overall quality, scientific accuracy, and/or legal conclusions, but this SMG does not require in-depth review of the article for those purposes, and all review must be conducted within the 30-day review period.

9. After allowing 30 days for the supervisory review, the employee may then submit the article for publication, or make the presentation, in all cases with the required disclaimer (as described below). Even if the employee has not received comments from the supervisor, the employee is responsible for ensuring that he or she complies with all legal and ethical requirements, including the duty to protect nonpublic information from public disclosure.

10. During the 30-day review period, the supervisor and employee may mutually decide that the employee will complete or finalize the publication or speech as assigned work rather than an outside activity. In that event, the employee may decide to withdraw the article from the 30-day review process for non-assigned FDA-related articles or speeches by submission of a written notification (e.g., an e-mail) to his or her supervisor.

11. All non-assigned FDA-related articles or speeches (including those that began as assigned work but were not completed or finalized as assigned work) must include the following disclaimer when published or presented: "This [article/speech/presentation/ book chapter] reflects the view of the author and should not be construed to represent FDA's views or policies." The disclaimer must be prominently displayed as part of its published or presented form. For a non-assigned FDA-related speech, the employee must preface his or her substantive remarks with the disclaimer and prominently include the disclaimer in any written materials provided as part of the speech.

7. EFFECTIVE DATE

The guide is effective February 2, 2011.

8. Document History - SMG 2126.3, Review of FDA-Related Articles and Speeches

STATUS (I, R, C)	DATE APPROVED	LOCATION OF CHANGE HISTORY	CONTACT	APPROVING OFFICIAL
Initial	01/25/2011	N/a	OC/OCS	Jesse L. Goodman, M.D., M.P.H., Chief Scientist and Deputy Commissioner for Science and Public Health

[1]Under 5 CFR 5501.106(d), an employee must obtain written approval before, among other things, engaging in teaching, speaking, writing, or editing that deals in significant part with (1) a current or recent assignment of the employee's or (2) the agency's ongoing or announced activities, programs, or operations. Another example of a regulation that could apply is 5 CFR 2635.807(a) (prohibiting, inter alia, an FDA employee from receiving compensation from any source other than the government for teaching, speaking, writing, or editing under certain circumstances).

Page Last Updated: 01/26/2011
Note: If you need help accessing information in different file formats, see Instructions for Downloading Viewers and Players.

Links on this page:

1. /downloads/AboutFDA/ReportsManualsForms/StaffManualGuides/UCM241191.pdf

Exhibit Y

Expert Report of Lawrence Goldkind, M.D.

INTRODUCTION

I have been asked by defense counsel in this matter to render an opinion concerning FDA's position on the labeling of incretin-based drugs with respect to pancreatic cancer.

BACKGROUND

A. Education and Employment Background

I am a medical doctor with specialty training in internal medicine and gastroenterology. I am certified in Internal Medicine and Gastroenterology by the American Board of Internal Medicine, and I have practiced medicine for over 30 years. I received my undergraduate degree from the University of Pennsylvania, *summa cum laude*, and was elected into Phi Beta Kappa. I earned my medical degree at the University of Maryland, where I did my training in internal medicine. I then completed a nutrition research fellowship at Harvard University and a gastroenterology fellowship at Boston University.

I practiced medicine in Tampa, Florida for 11 years before joining the United States Food and Drug Administration (FDA) in 1998 as a Medical Officer in the Division of Gastrointestinal and Coagulation Drug Products in the Center for Drug Evaluation and Research (CDER). After serving as a Medical Officer for two years, I was promoted to the positions of Team Leader (in 2000) and Acting

Division Director of the Division of Analgesic, Anti-inflammatory and Ophthalmic Drug Products (DAAODP) (in 2001). From 2001 to 2003, I served as Acting Director of DAAODP. While I was at FDA, I also held a position as a Staff Physician at the National Naval Medical Center (now the Walter Reed National Military Medical Center). I left FDA in 2003 to take up a position as an Assistant Professor of Gastroenterology and Medicine at the Uniformed University of Health Sciences School of Medicine in Bethesda, Maryland, continuing as an attending physician at Walter Reed. After leaving FDA, I also started a consulting practice, consulting with clients on pharmaceutical development and regulatory issues.

I currently teach medical students, internal medicine trainees and gastroenterology trainees. I provide medical care to active-duty military personnel and their families, as well as retired officers and members of the Legislative, Executive, and Judicial branches of the Federal Government. Over the course of my career, I have treated numerous patients with diabetes, pancreatitis, and pancreatic cancer.

A list of materials I have considered in reaching the opinions expressed in this report is attached as Exhibit A. My *curriculum vitae*, which includes a list of publications I have authored, is attached as Exhibit B. A list of cases in which I have testified at trial or at deposition in the past four years is attached as Exhibit C. I am being compensated at my usual hourly rate of $500.

B. FDA Experience

At FDA, I served extensively as a primary reviewer, as well as supervisory reviewer, of many types of regulatory submissions, including the following: Investigational New Drug (IND) applications; clinical protocols; clinical study reports; adverse event reports; New Drug Applications (NDAs); supplemental NDAs (sNDAs); submissions from sponsors for labeling changes; post-marketing periodic safety update reports; annual reports; and citizens' petitions.

On many occasions, I was also the senior FDA supervisor involved in labeling discussions and industry meetings (including pre-IND meetings, end-of-phase 2 meetings, pre-NDA meetings and post-nonapproval meetings with pharmaceutical sponsors). I have presented on behalf of the Agency at multiple FDA advisory committee meetings, including on labeling issues.

As a Deputy Division Director and Acting Division Director within the Office of New Drugs (OND) at CDER, I had signatory authority for approving drug labels and post-marketing revisions to labeling for approved products. As a Medical Officer and Division Director at FDA, my responsibilities routinely included evaluating safety-related questions based on data analyses performed by FDA staff and/or submitted by sponsors.

OPINIONS

My opinions are based on the materials identified in Exhibit A, and on my education, training, and experience as a physician and gastroenterologist, as well as my FDA experience, including my knowledge of FDA regulations, policies, review procedures, practices, and guidances. I hold the opinions expressed herein to a reasonable degree of scientific and regulatory certainty. I reserve the right to testify in my areas of expertise in response to the opinions of Plaintiffs' experts. I also reserve the right to supplement the opinions included in this report based on new information.

A. FDA's Role in Development, Approval and Labeling of Prescription Drugs

FDA has primary responsibility for regulating prescription drugs in the United States. Both before and after approval, FDA devotes extensive resources and energy to ongoing review of the safety of prescription drugs. FDA typically has in its possession safety data that it has accumulated from the universe of investigational and approved drugs submitted for FDA's consideration—data that are not available to any one sponsor or to the public. FDA may also have data from its own internal studies and analyses.

FDA's review, approval, and oversight process is governed by a comprehensive set of regulations that include very specific guidelines on

appropriate product labeling. FDA considers labeling to be the centerpiece of risk management for prescription drugs. *See generally* 71 Fed. Reg. 3922 (Jan. 24, 2006).

Once a drug is marketed, FDA and the sponsor continue to monitor and investigate the drug's risks and benefits. Specific regulations and guidances govern the continued collection, review, and submission of safety data to FDA. FDA regulations set forth certain information, such as post-marketing adverse event reports, periodic reports, and annual reports, that drug sponsors are required to submit to FDA. If FDA determines that further data are needed to assess a potential safety issue, FDA can request such data from the sponsor and/or require that the sponsor conduct additional studies. FDA can also conduct its own studies as part of its post-marketing oversight of pharmaceuticals.

FDA has a full-time staff that is dedicated to monitoring drug safety. Each division within OND has a deputy division director for safety (with supporting staff) who monitors post-marketing safety within the division that has specific expertise in the disease being treated and knowledge regarding alternative therapies and their associated risks. For example, FDA has reviewed safety information on approximately 50 investigational incretin-based drugs.

In addition, the Office of Surveillance and Epidemiology (OSE) has divisions that deal with the various scientific elements of risk assessment, such as

epidemiology, causality assessment, and risk communication. OSE and the review divisions in OND communicate through the deputy division director for safety within the review division of OND.

FDA has extensive authority to take action concerning a drug and its labeling after it has been approved. FDA may instruct the sponsor to revise its label to add information necessary to inform health care providers fully about the risks and benefits of the medication. Under certain circumstances defined in FDA regulations, sponsors may submit label changes to FDA through a prior approval supplement (PAS) or changes being effected (CBE) supplement. *See* 21 C.F.R. §§ 314.70(b); 314.70(c)(6)(iii). All label changes must be approved by FDA. FDA makes the final determination about the content, placement, and language of the information in the product label in accordance with the regulations. FDA has the authority to make the final determination in order to ensure that the product labeling includes appropriate safety information, but does not include information about risks that are speculative or unsubstantiated. Inclusion of information about risks that are speculative or unsubstantiated may have a negative effect on patient safety—by deterring physicians from prescribing a beneficial medication—and may decrease the usefulness of the product labeling by diluting clinically meaningful information. If a sponsor does not comply with FDA's instruction, FDA can withdraw its approval of the drug and/or take actions to declare the drug

misbranded and remove the drug from the market. *See* 21 U.S.C. § 331(a); 21 U.S.C. § 334(a); 21 U.S.C. § 352(a); 21 C.F.R. § 314.150 (b) (3).

B. FDA Has Taken an Official Position on the Pancreatic Safety of Incretin-Based Medications and Their Labeling

In March 2013, FDA issued a safety communication in which it announced that it would review data that had raised questions about the pancreatic safety of incretin-based therapies and would communicate its final conclusions and recommendations when its review was complete. In its safety communication, FDA advised health care professionals to continue to follow the prescribing recommendations in the labels for these medications.

In February of 2014, FDA and the European Medical Agency (EMA) co-authored an article in the *New England Journal of Medicine* concerning the safety profile and labeling of incretin-based therapies with respect to pancreatitis and pancreatic cancer. *See* Amy G. Egan, et al., *Pancreatic Safety of Incretin-Based Drugs—FDA and EMA Assessment*, N. Eng. J. Med. 794, 795 (Feb. 27, 2014) (the "Assessment"). A month later, FDA issued a response rejecting a Citizen's Petition, which had asked that one incretin-based product, Victoza, be taken off the market in part because of allegations about a potential connection with pancreatic cancer. *See* FDA's response to the Citizen's Petition: Docket No. FDA-2012-P-0404 (March 25, 2014) (FDA's Citizen Petition Response).

The Assessment and FDA's Citizen Petition Response each represents FDA's official position. Per the pertinent FDA staff manual, statements made by FDA staff can be made in connection with "FDA-assigned work" or not. *See* FDA Staff Manual, External Relations: Review of FDA Related Articles and Speeches: SMG 2126.3 (Feb. 2011) (FDA Staff Manual).[1] A publication that is not based on "FDA-assigned work" must contain the following disclaimer: "This [article/speech/presentation/ book chapter] reflects the views of the author and should not be construed to represent FDA's views or policies." FDA Staff Manual, § 6.B.11. If a publication is based on "FDA-assigned work," it may or may not require a disclaimer, at the discretion of the supervisory authority. If FDA-related work does not represent Agency views, it requires a disclaimer. If a publication does not contain the above disclaimer, it represents the Agency's official position. *See id.* § 6.A. FDA has established a rigorous review and clearance process for FDA-assigned publications. *See id.* I personally published articles while at the FDA. In my experience, FDA adheres strictly to the process outlined in the Staff Manual.

I have reviewed the Assessment, and it is FDA-assigned work and represents the official position of FDA. The article does not contain a disclaimer that the

[1] The manual is available at: <http://www.fda.gov/AboutFDA/ReportsManualsForms/StaffManualGuides/ucm241089.htm>.

expressed views may not represent the official views of the Agency. The publication is titled "FDA and EMA Assessment," and extensively details FDA's evaluation of a potential association between pancreatic cancer and incretin-based therapies, and explicitly concludes that "FDA and the EMA believe that the current knowledge is adequately reflected in the product information or labeling" and that "[b]oth agencies agree that assertions concerning a causal association between incretin-based drugs and . . . pancreatic cancer . . . are inconsistent with the current data." Assessment at 796.

FDA's Citizen's Petition Response is further evidence of FDA's careful review of the safety of incretin-based drugs, including the allegations of a possible association between incretin-based therapies and pancreatic cancer. *See* FDA's Citizen's Petition Response generally and at 26. This response also represents the official Agency position.

C. FDA Publicized Its Official Conclusions from Its Comprehensive Evaluation of the Scientific Evidence Relating to Pancreatic Cancer and Incretin-Based Therapies.

The Assessment reflects FDA's robust and comprehensive evaluation of the scientific evidence relating to pancreatic cancer and incretin-based therapies. As the Assessment itself indicates, FDA conducted a "comprehensive evaluation" of a potential safety signal for pancreatic cancer and incretin-based therapies. *See* Assessment at 795.

The breadth and depth of FDA's review was extensive, and included FDA's own independent work on the safety profile of incretin-based drugs. In my opinion, FDA's decision to undertake such an extensive written review for purposes of publishing the results to the public is significant. It evidences FDA's commitment to relaying to prescribing physicians FDA's considered views on the safety profile of these drugs. FDA's review included the following:

- Review of multiple sponsor-submitted and published studies including epidemiologic and post mortem-human studies. FDA even communicated with the authors of a published study, asking them to provide the Agency with more detailed information about the study methodology. It further asked the authors to provide the primary material (histology slides) for detailed review by Agency toxicologists.
- Reanalysis of nonclinical toxicology studies, including having FDA toxicologists review primary materials. This review included over 250 toxicology studies conducted in nearly 18,000 animals. These studies included studies in two species treated for the full life expectancy of the animals at doses well beyond human therapeutic doses.
- FDA issued a post-marketing requirement to the sponsors of three incretin-based therapies approved prior to 2013 using the specific authority of the Food and Drug Administration Amendments Act of 2007 to require animal

studies in various models, including engineered models of diabetes that may magnify, or were thought to magnify, the animals' potential to develop cancer or precancerous lesions. FDA took the extra step of having its own staff pathologists review the primary source material (the histology slides) from one of the studies. In addition, FDA mandated epidemiologic studies be performed by the sponsors of these medications.

- FDA performed its own toxicology studies on both healthy rodents and rodents with chemically-induced pancreatitis in the setting of a diabetic animal model in two species.
- Reanalysis of over 200 clinical trials that involved over 40,000 subjects, of which over 8,000 were exposed for over a year.
- Review of two large, FDA-mandated studies of two DPP-4 inhibitors that included over 20,000 subjects.

Notably, in evaluating the safety of incretin-based therapies, FDA had more information about these products than any one of the drug sponsors. Based on my experience, it is very significant that FDA chose to publish its findings in this manner, and it is also significant that FDA and EMA chose to collaborate to the extent seen here. The fact that FDA took this deliberate step demonstrates the importance FDA attributed to the issue and to ensuring that its findings were clearly communicated to and understood by the public.

FDA concludes the following:

> [T]he FDA and the EMA have explored multiple streams of data pertaining to a pancreatic safety signal associated with incretin-based drugs. Both agencies agree that assertions concerning a causal association between incretin-based drugs and pancreatitis or pancreatic cancer, as expressed recently in the scientific literature and in the media, are inconsistent with the current data. The FDA and the EMA have not reached a final conclusion at this time regarding such a causal relationship. Although the totality of the data that have been reviewed provides reassurance, pancreatitis will continue to be considered a risk associated with these drugs until more data are available; both agencies continue to investigate this safety signal. The FDA and the EMA believe that the current knowledge is adequately reflected in the product information or labeling and further harmonization among products is planned in Europe. Ongoing strategies include systematic capture of data on pancreatitis and pancreatic cancer from cardiovascular outcome trials and ongoing clinical trials, which should facilitate meta-analyses, and accumulation of further knowledge regarding these signals in the future.

Assessment at 796.

FDA undertook its Assessment because of assertions "expressed recently in the scientific literature and in the media" concerning a causal relationship between incretin-based therapies and pancreatic cancer. *Id.* Thus, the key question before FDA was whether the labeling should include a reference to pancreatic cancer. FDA's official conclusion in the Assessment that the labeling was adequate is a rejection of the suggestion that the label should be changed. If FDA had thought that a label change was appropriate, it would have required one at the time of its comprehensive Assessment, if not earlier. FDA reaffirmed its conclusion a month

later when it expressly rejected the Victoza Citizen's Petition, and again when FDA subsequently approved additional medications in the class without any reference to pancreatic cancer (as discussed below).

The Assessment states that FDA and EMA have not "reached a final conclusion at this time regarding a causal relationship" and "continue to investigate this safety signal." Assessment at 796. This statement simply reflects that, as a matter of routine practice, FDA continuously monitors every medication for new or evolving information as long as a drug is on the market. Accordingly, the Assessment reflects FDA's determination that, as of February 2014, the available scientific evidence is neither consistent with, nor supports, a causal association between incretin-based therapies and pancreatic cancer.

D. FDA Has Reiterated Its Position by Rejecting the Victoza Citizen's Petition and Approving Labeling for New Incretin-Based Drugs that Does Not Warn of Pancreatic Cancer.

In April 2012, Public Citizen filed a Citizen's Petition to remove Victoza from the market. In the petition, Public Citizen raised a number of potential issues, including pancreatic cancer. In March 2014, after a comprehensive review of the evidence, FDA rejected the Petition in its entirety. On pancreatic cancer, FDA stated that its review, which included evaluation of spontaneous adverse event reports, "found no new evidence regarding the risk of pancreatic cancer . . . that would support any changes to the current approved labeling." FDA's Response to

Citizen's Petition at 26. This FDA conclusion reiterates FDA's official position that incretin-based drugs should not be labeled to warn for pancreatic cancer.

Since it rejected the Citizen's Petition, FDA has approved two additional incretin-based therapies, Tanzeum (albiglutide) (April 2014) and Trulicity (dulaglutide) (September 2014). In each case, FDA approved product labeling without any reference to pancreatic cancer. Certainly, FDA would have required that these labels warn about pancreatic cancer if it had believed such a warning was appropriate for incretin-based therapies.

CONCLUSION

Based on my years of experience at FDA and generally in the regulation of pharmaceutical products, it is my opinion (as set forth in more detail above) that FDA's official conclusion in FDA's Assessment and Citizen's Petition Response is that the labeling for incretin-based drugs is adequate and that the data do not support including a reference to pancreatic cancer in the product labels.

I reserve my right to supplement this report.

Executed on December 15, 2014.

Lawrence Goldkind, M.D.

Exhibit Z

Rebuttal Expert Report of Lawrence Goldkind, M.D.

INTRODUCTION

I submitted an expert report in this matter on December 15, 2014. I have since been asked to review the expert reports of G. Alexander Fleming, M.D. and David Madigan, Ph.D. My review of these reports does not change the opinions that I expressed in my opening report.

I have been asked to focus in particular on the significance of FDA's conclusion that the labeling for incretin-based drugs is adequate with respect to pancreatic cancer. Contrary to Dr. Fleming's assertions, FDA has very clearly and thoroughly assessed whether there is evidence of a causal association between incretin-based drugs and pancreatic cancer, has determined that the scientific data do not support such an association, and has confirmed that it would not be appropriate to include pancreatic cancer in the labeling of incretin-based drugs.

In preparing this second report, I considered the materials listed in Exhibit A to my first report, together with the additional materials listed in Exhibit D to this report. My opinions are also based on my FDA experience, including my experience as an Acting Division Director, in which position I had authority to approve and reject medications for marketing in the U.S., and to require, approve and reject changes to the labeling for prescription medications.

OPINIONS

A. The Assessment represents FDA's official position.

As I noted in my opening report, in February 2014, FDA and the European Medicines Agency (EMA) co-authored and published in the *New England Journal of Medicine* their conclusions concerning the safety profile and labeling of GLP-1 receptor agonists (such as Byetta and Victoza) and DPP-4 inhibitors (such as Januvia and Onglyza) with respect to pancreatitis and pancreatic cancer. *See* Amy G. Egan, et al., *Pancreatic Safety of Incretin-Based Drugs—FDA and EMA Assessment*, N. Eng. J. Med. 794 (Feb. 27, 2014) (the Assessment). The Assessment represents FDA's official position that the labeling for both classes of incretin-based drugs is adequate and that the data do not support including pancreatic cancer in the product labels. Its publication in one of the most respected and frequently cited peer-reviewed medical journals in the world (with an impact factor of 54.42, highest among general medical journals) attests to the importance FDA placed on the article. In my experience at FDA, FDA has on a number of occasions chosen the *New England Journal of Medicine* to publish its conclusions on safety topics when it has wanted to communicate its opinions to physicians on product labeling, especially when a safety issue has been the subject of public discussion.

Consistent with its conclusions in the *New England Journal of Medicine*, FDA has since denied the Citizen's Petition concerning Victoza and has approved labeling for a number of additional incretin-based drugs without the labeling containing any reference to pancreatic cancer. Most recently, on December 23, 2014, FDA approved the labeling for a higher dose (3 mg) of liraglutide for the treatment of obesity (brand name Saxenda) without any reference to pancreatic cancer.[1]

Dr. Fleming suggests that if one of the manufacturers had submitted a CBE to add pancreatic cancer to its product's labeling, FDA would not have prohibited it. Fleming Report at 107. A label change to include reference to pancreatic cancer would be appropriate only if the scientific evidence satisfied the regulatory standards for inclusion in the label. *See* 21 C.F.R. §§ 201.57(c)(6)-(7). FDA's analysis of this issue, as reflected in the Assessment, represents the type of safety review that would have been performed in response to a Changes Being Effected (CBE) or Prior Approval Supplement (PAS) review. The Assessment reflects a

[1] As part of the approval process for Saxenda, FDA reviewed the data and prepared a briefing book for the September 2014 Saxenda Advisory Committee meeting. In its briefing book, FDA explicitly stated, citing to the Assessment, that "Both FDA and the European Medicines Agency (EMA) have explored multiple data streams to evaluate pancreatic toxicity as a potential drug safety signal, which to date, do not support pancreatic cancer as an incretin mimetic-mediated event." Pharmacovigilance Review at 313, available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM413317.pdf.

thorough internal safety review consistent with FDA's standard practice for regulatory decision-making regarding drug labeling: first with analysis of preclinical toxicology studies, followed by human data generated in the clinical development of the drug under discussion, and then followed further by additional epidemiological data. Here, FDA's decision-making involved reviewing and re-evaluating hundreds of studies, including clinical, non-clinical, observational, and post-mortem studies. FDA also directed sponsors to conduct additional studies specifically to evaluate potential pancreatic effects. FDA staff reviewed the source material from one of these studies and also took the extra step of conducting additional toxicology studies.

Further, FDA's Assessment in February 2014 was the culmination of a years' long evaluation.[2] Based on the conclusions FDA reached in 2014, there is no reason to speculate, and no basis to believe, that FDA would have taken a different approach or reached a different conclusion at a prior point in

[2] For examples, see the FDA Approval Letter (Byetta for use as monotherapy), Oct. 30, 2009 (requiring Amylin to conduct pancreatic safety studies of Byetta, including epidemiologic queries to assess relative risk of pancreatic cancer and thyroid neoplasm among patients using Byetta and patients using metformin or glyburide); *Byetta Safety Update for Healthcare Professionals, Food and Drug Administration* (Nov. 9, 2011), http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm190406.htm) (announcing same); *FDA investigating reports of possible increased risk of pancreatitis and pre-cancerous findings of the pancreas from incretin mimetic drugs for type 2 diabetes*, Food and Drug Administration (March 14, 2013), http://www.fda.gov/Drugs/DrugSafety/ucm343187.htm); and Megan Brooks, *FDA Sides With EMA on Incretin Diabetes Drugs*, MEDSCAPE MEDICAL NEWS (August 1, 2013).

time. Viewing the Assessment in light of my experience with FDA decision-making relating to labeling, it is my opinion that if a sponsor had asked FDA to consider adding pancreatic cancer to the labeling, FDA would have conducted the same analysis as it has now conducted.

B. FDA's review of the pancreatic safety of incretin-based drugs.

In reviewing the role played by FDA in ensuring the adequacy of drug labeling, Dr. Fleming states that "drug companies, not FDA, are responsible for alerting the medical community, potential prescribers and patients to the risks associated with their drugs." Fleming Report at 16. While it is true that drug manufacturers have responsibility for the content of their labels, Dr. Fleming downplays FDA's central role in drug labeling. All labeling and labeling changes must ultimately be approved by FDA.

Dr. Fleming also understates the resources FDA brings to bear in ensuring drug safety, including the adequacy of drug labeling. FDA has substantial authority to gather data from sponsors, as Dr. Fleming notes. *See* Fleming Report at 19-21. For example, FDA regulations set forth certain information, such as post-marketing adverse event reports, periodic reports, and annual reports, that drug sponsors are required to submit to FDA. If FDA determines that further data are needed to assess a potential safety issue, FDA can (and regularly does) request such data from the sponsor. FDA can also conduct its own studies and analyses.

In this instance in particular, FDA has access to data far beyond the reach of any individual sponsor of an incretin-based drug. Sponsors typically do not have access to data from their competitors and may not have access to all data collected in studies conducted by FDA and independent researchers. FDA, though, has accumulated data from the sponsors of all incretin-based therapies, conducted its own studies, and gathered information from independent researchers, and, therefore, can analyze significantly more safety data than any one sponsor.

C. FDA's conclusions with respect to pancreatic cancer.

Dr. Fleming contends that the FDA would permit labeling on pancreatic cancer. *See* Fleming Report at 107. However, contrary to Dr. Fleming's view, FDA's overriding concern is the *adequacy* of a drug's label, and changes to the Adverse Reactions or Warnings and Precautions section of a label are only appropriate where the scientific evidence satisfies the regulatory standards for a causal association between the drug and the adverse reaction. *See* 21 C.F.R. §§ 201.57(c)(6)-(7). In assessing whether the science supports a change for the labeling with respect to pancreatic cancer, FDA employs the same standards to assess whether to *mandate* a label change and whether to *permit* a label change.

In FDA's view, the term "adequate" as applied to drug labeling is not a minimum FDA requirement for labeling, such that a sponsor is free to provide different labeling. In this instance, when FDA completed its investigation and

found that the labeling was adequate and reflected the current state of knowledge, FDA was stating its official regulatory position on the issue.

Dr. Fleming's theory that FDA would allow manufacturers to add reference to pancreatic cancer in the Adverse Reactions section of the labeling simply because other adverse events (such as pancreatitis) are included, Fleming Report at 103-106, is also incorrect. FDA specifically has addressed whether the labeling should reference pancreatic cancer and has concluded that it should not. Moreover, each adverse event is different—as are the data that relate to the potential interaction between each drug and the specific adverse event in question—and for this reason, each adverse event has to be considered individually. What constitutes appropriate labeling regarding pancreatitis is a different question than what constitutes appropriate labeling regarding pancreatic cancer, as FDA confirmed in its Assessment. FDA considered both pancreatitis and pancreatic cancer, and decided that the current labeling for each disease was appropriate. The Assessment makes clear that FDA distinguished between the two disease states in its analysis. Had FDA believed that the decision to include a warning about pancreatitis in the label was a reason to include information about pancreatic cancer, it would have said so in the Assessment.

Dr. Fleming further states that "FDA has no established policy for *prohibiting* warnings and risk information." Fleming Report at 89. Dr. Fleming

contends, despite the plain language of FDA's regulations, that FDA would permit sponsors to add warnings even where FDA itself has determined that the scientific data do not support a label change. *Id.* That is simply not true. FDA is concerned with preventing drug labeling that overwarns of possible risks, as overwarning waters down risk information that is scientifically sound, may discourage physicians from prescribing a medication to patients who might benefit from using it, and may cause physicians to prescribe other drugs that may be less effective and/or less safe for particular patients. Information that is not accurate or supported by at least some evidence of a causal association is not useful to physicians. For this reason, as described in 71 FR 3922, 3935, FDA has authority to declare a drug misbranded if it contains information that does not satisfy the regulatory standards for causal association.

Dr. Fleming also says that "FDA has now on several occasions informed the public that it believes there is a plausible causal association between incretin mimetics and pancreatic cancer in humans." Fleming Report at 8. I am aware of no such statement, and the documents Dr. Fleming cites reflect no such statement, by FDA. Dr. Fleming cites the March 2013 Drug Safety Communication, which states only that FDA was "evaluating" a potential signal for precancerous findings, not that FDA believed it was plausible that incretin-based drugs caused pancreatic cancer. FDA specifically stated that "FDA has not concluded these drugs may

cause or contribute to the development of pancreatic cancer."[3] Dr. Fleming also incorrectly cites the NEJM Assessment itself, which states that a causal association is "inconsistent with the current data." Assessment at 796.

Finally, Dr. Fleming's report does not address the basic fact that FDA is under no obligation to wait on drug manufacturers to act. If FDA believes a labeling change is necessary, it is required by law to mandate the change, and it has numerous tools, including 21 C.F.R. § 1.21(b), to implement the change. Indeed, another regulation, 21 CFR § 314.70(c)(6)(iii)(E), authorizes FDA to request that a sponsor submit a CBE. Given the FDA's regulatory mandate and consistent with my FDA experience, FDA certainly would not wait for sponsors to act if it believed that there were some basis to conclude that incretin-based drugs are causally associated with a deadly disease such as pancreatic cancer.

FDA is the regulatory body tasked with reviewing drug safety and labeling. It has reached its conclusion. That conclusion is reflected in the current labeling for incretin-based drugs.

[3] FDA also made plain in the Communication that "patients should continue to take their medications as directed," and that "health care professionals should continue to following the prescribing recommendations in the drug labels."

D. FDA's use of adverse event reports.

Dr. Fleming suggests that adverse event reports regarding pancreatic cancer and incretin-based drugs are sufficient to support a label change to include pancreatic cancer. *See* Fleming Report at 106. FDA repeatedly has rejected this view. Specifically as to whether adverse event reports of pancreatic cancer and the drugs at issue here constitute evidence of a causal association, FDA stated in its Assessment that: "Although the disproportionate spontaneous reporting of adverse events is commonly interpreted as a safety signal, there are inherent limitations in the ability to establish causal relationships, including the evaluation of events with high background rates, long latency periods, or a possible contribution by the disease itself." Assessment at 795. FDA reiterated its view in its response to the Citizen's Petition, stating that "[a]nalysis of drug-related risk utilizing [the adverse event reporting database] data does not provide strong evidence of risk when the adverse event (i.e., pancreatic cancer) occurs commonly in the background untreated population and has a long latency period." FDA's Response to Citizen's Petition at 26.

FDA was aware of adverse event reports of pancreatic cancer associated with incretin-based drugs, specifically considered those reports as part of its Assessment and response to the Citizen's Petition, and determined that the reports were of limited value in assessing a potential causal association between incretin-

based drugs and pancreatic cancer. FDA concluded in its response to the Citizen's Petition that there was "no new evidence regarding the risk of pancreatic carcinoma . . . that would support any changes to the current approved labeling." FDA has carefully monitored adverse event reports, and decided as recently as December 23, 2014, that the labeling for an incretin-based drug, Saxenda, should not include a reference to pancreatic cancer.

Dr. Fleming's suggestion that a safety signal for pancreatic cancer based on adverse events would itself be a basis for labeling changes is also incorrect. FDA has made plain that a safety signal generated through adverse event data mining is simply an indication that a drug *might* be associated with a particular risk and that further study is warranted. In general, a safety signal is not itself evidence of a causal association between a drug and an adverse event. FDA's Guidance on Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (March 2005) (Guidance on Good Practices)[4] clarifies that signal generation is the only the *first step* in pharmacovigilance and indicates the need for further investigation before any conclusions are drawn. "After a signal is identified, it should be further assessed to determine whether it represents a potential safety risk and whether other action should be taken." Guidance on Good Practices at 4.

[4] Available at http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126834.pdf.

The Guidance on Good Practices also restates the regulatory authority of FDA specifically related to the assessments of safety signals. While the sponsor is expected to perform pharmacovigilance and assess safety signals, "FDA will make its own assessment of the safety risk posed by the signal in question, taking into account the information provided by the sponsor and any additional relevant information known to the FDA (e.g. information on other products in the same class) and communicate its conclusion to the sponsor." Guidance on Good Practices at 18.

E. FDA's statements in the *NEJM* represent FDA's conclusions.

Dr. Fleming contends that the Assessment merely reflects FDA's "ongoing interest . . . in the safety of incretin mimetics" because the Assessment indicates that FDA is continuing to investigate the issue. *See* Fleming Report at 7-8. As I explained in my opening report, however, this statement by FDA simply reflects that, as a matter of routine practice, FDA continuously monitors *every* medication for new or evolving information as long as a drug is on the market. Indeed, FDA was quite clear in stating that it had reached a conclusion. FDA expressly stated that its investigations were "now complete" and that its belief—and that of the EMA—that the labels are "adequate" is based on "current knowledge." Assessment at 795-96.

In March 2013, FDA announced that it would conduct a "comprehensive evaluation" of the pancreatic safety of incretin-based drugs. The resulting Assessment declared that FDA's "comprehensive evaluation" was "now complete," and that the available scientific data did not support including reference to pancreatic cancer in the drug labels. Assessment at 795. Dr. Fleming states that absent "any actual submission of a label change" that is rejected by FDA, he does "not believe there is any sound basis on which to conclude the FDA would prohibit a pancreatic cancer warning or adverse reaction supplement, if proposed by the drug's manufacturer." Fleming Report at 90-91. I disagree. FDA's publication of the Assessment, its Response to the Citizen's Petition and the multiple approvals for incretin-based drugs together provide at least as strong an indication of FDA's position with respect to the adequacy of labeling as would a rejection of a CBE. FDA either makes a determination that cautionary language belongs in the labeling or FDA makes a determination that it does not belong.

CONCLUSION

Based on my years of experience at FDA and generally in the regulation of pharmaceutical products, it remains my opinion (as set forth in more detail above and in my original report) to a reasonable degree of scientific and regulatory certainty that FDA's official conclusion is that the labeling for incretin-based drugs

is adequate and that the "current knowledge" does not support reference to pancreatic cancer in the product labels.

I reserve my right to supplement this report.

Executed on April 13, 2015.

Lawrence Goldkind, M.D.

EXHIBIT D

Supplemental Materials Reviewed

1. Expert Report of G. Alexander Fleming, M.D.
2. Expert Report of David Madigan, Ph.D.
3. Labeling for Saxenda (liraglutide 3 mg)
4. Food and Drug Administration Briefing Book for Saxenda Advisory Committee Meeting (Sept. 11, 2014).
5. Documents Bates-labeled FDAJAN0000000001-FDAJAN0000021737 and NNI-FDA-FOIA1-NNI-FDA-FOIA12364
6. Approval Letter for Byetta, Food and Drug Administration (Oct. 30, 2009)
7. Food and Drug Administration, *Byetta Safety Update for Healthcare Professionals* (Nov. 9, 2011)
8. Food and Drug Administration, *FDA investigating reports of possible increased risk of pancreatitis and pre-cancerous findings of the pancreas from incretin mimetic drugs for type 2 diabetes* (March 14, 2013)
9. Megan Brooks, *FDA Sides With EMA on Incretin Diabetes Drugs*, MEDSCAPE MEDICAL NEWS (August 1, 2013)
10. Butler AE, Campbell-Thompson M, Gurlo T, Dawson DW, Atkinson M, Butler PC. *Marked expansion of exocrine and endocrine pancreas with incretin therapy in humans with increased exocrine pancreas dysplasia and the potential for glucagon-producing neuroendocrine tumors*. DIABETES 2013;62:2595-2604
11. European Medicines Agency, *Assessment report for GLP-1 based therapies* (July 25, 2013)
12. Engel SS, Round E, Golm GT, Kaufman KD, Goldstein BJ, *Safety and tolerability of sitagliptin in type 2 diabetes: pooled analysis of 25 clinical studies*. DIABETES THER 2013;4:119-145
13. Scirica BM, Bhatt DL, Braunwald E, et al., *Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus*. N ENGL J MED 2013;369:1317-1326
14. White WB, Cannon CP, Heller SR, et al., *Alogliptin after acute coronary syndrome in patients with type 2 diabetes*. N ENGL J MED 2013;369:1327-1335